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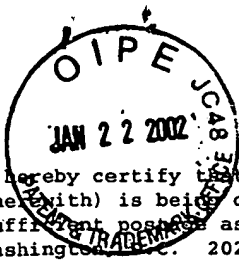
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F. Aaron Dubberley  
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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1614

Jean Ackermann, et al.

Serial No.: 09/939,872

Filed: August 27, 2001

For: **2,3-OXIDOSQUALENE-LANOSTEROL CYCLASE INHIBITORS**

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December 18, 2001

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Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

<u>Country</u>	<u>Application No.</u>	<u>Filing Date</u>
Europe	00119677.3	September 9, 2000

Respectfully submitted,

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Enclosures  
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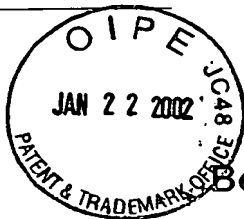
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Bescheinigung

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Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

00119677.3

Der Präsident des Europäischen Patentamts;  
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets  
p.o.

I.L.C. HATTEN-HECKMAN

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**Blatt 2 der Bescheinigung  
Sheet 2 of the certificate  
Page 2 de l'attestation**

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Application no.:  
Demande n°: 00119677.3

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Date de dépôt: 08/09/00

Anmelder:  
Applicant(s):  
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SWITZERLAND

Bezeichnung der Erfindung:  
Title of the invention:  
Titre de l'invention:  
Novel piperidine derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

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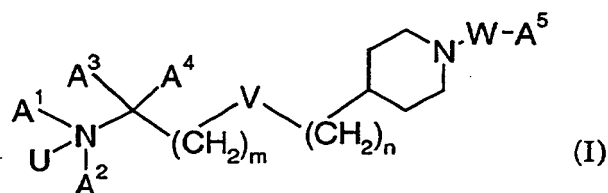
F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

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08. Sep. 2000

Case 20757

Novel Piperidine Derivatives

The present invention is concerned with novel piperidine derivatives, their manufacture and their use as medicaments. In particular, the invention relates to compounds of the formula (I)



5

wherein

U is O or a lone pair,

V is O, -CH<sub>2</sub>-, -CH=CH-, or -C≡C-,

m and n independently from each other are 0 to 7 and m+n is 0 to 7,

10 W is CO, COO, CONR<sup>1</sup>, CSO, CSNR<sup>1</sup>, SO<sub>2</sub>, or SO<sub>2</sub>NR<sup>1</sup>, with the proviso that:a) V is not -CH<sub>2</sub>- if W is CO,b) m+n is 1 to 2 if V is -CH<sub>2</sub>- and W is SO<sub>2</sub>,c) m=n=0 if V is -CH=CH- and W is CO or SO<sub>2</sub>,

d) m is 1 to 7 if V is O,

15 e) n is 1 to 6 or m+n is 1 to 3 if V is O and W is CO or SO<sub>2</sub>,A<sup>1</sup> is H, lower-alkyl or lower-alkenyl,A<sup>2</sup> is cycloalkyl, cycloalkyl-lower-alkyl, lower-alkenyl, lower alkynyl, or lower-alkyl optionally substituted with hydroxy, lower-alkoxy or lower-alkoxy-carbonyl,

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- 2 -

$A^3$  and  $A^4$  are hydrogen or lower-alkyl, or

$A^1$  and  $A^2$  or  $A^1$  and  $A^3$  are bonded to each other to form a ring  
and  $-A^1-A^2-$  or  $-A^1-A^3-$  are lower-alkylene or lower-alkenylene, optionally  
substituted by  $R^2$ , in which one  $-CH_2-$  group of  $-A^1-A^2-$  or  $-A^1-A^3-$  can  
optionally be replaced by  $NR^3$ , S, or O,

$A^5$  is lower-alkyl optionally substituted with halogen, lower-alkenyl, lower-  
alkoxy-carbonyl-lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl, aryl-  
lower-alkyl, heteroaryl, or heteroaryl-lower-alkyl,

$R^2$  is lower-alkyl, hydroxy, hydroxy-lower-alkyl, or  $N(R^4, R^5)$ ,

$R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  independently from each other are hydrogen or lower-alkyl,  
and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

The compounds of the present invention inhibit 2,3-oxidosqualene-lanosterol  
cyclase (EC 5.4.99.) which is required for the cholesterol and ergosterol biosynthesis.  
Causal risk factors that directly promote the development of coronary and peripheral  
atherosclerosis include elevated low-density lipoprotein cholesterol (LDL-C), low high-  
density lipoprotein cholesterol (HDL-C), hypertension, cigarette smoking and diabetes  
mellitus. Other synergistic risk factors include elevated concentrations of triglyceride  
(TG)-rich lipoproteins, small, dense low-density lipoprotein particles, lipoprotein (a)  
(Lp(a)), and homocysteine. Predisposing risk factors modify the causal or conditional risk  
factors and thus affect atherogenesis indirectly. The predisposing risk factors are obesity,  
physical inactivity, family history of premature CVD, and male sex. The strong connection  
between coronary heart disease (CHD) and high LDL-C levels in plasma, and the  
therapeutic advantage of lowering elevated LDL-C levels are now well established (Gotto et  
al., Circulation 81, 1990, 1721-1733; Stein et al., Nutr. Metab. Cardiovasc. Dis. 2, 1992,  
113-156; Illingworth, Med. Clin. North. Am. 84, 2000, 23-42). Cholesterol-rich, sometimes  
unstable, atherosclerotic plaques lead to the occlusion of blood vessels resulting in an  
ischemia or an infarct. Studies with respect to primary prophylaxis have shown that a  
lowering of plasma LDL-C levels in plasma reduces the frequency of non-fatal incidences  
of CHD, while the overall morbidity remains unchanged. The lowering of plasma LDL-C  
levels in patients with preestablished CHD (secondary intervention) reduces CHD-  
mediated mortality and morbidity; metaanalysis of different studies shows that this  
decrease is proportional to the reduction of the LDL-C (Ross et al., Arch. Intern. Med. 159,  
1999, 1793-1802).

The clinical advantage of cholesterol lowering is greater for patients with

- 3 -

preestablished CHD than for asymptomatic persons with hypercholesterolemia. According to current guidelines patients who had survived a myocardial infarct or patients suffering from angina pectoris or another atherosclerotic disease a cholesterol-lowering treatment is recommended, with a target LDL-C level of 100 mg/dl.

5       Preparations such as bile acid sequestrants, fibrates, nicotinic acid, probucol as well as the statins (HMG-Co-A reductase inhibitors) such as simvastatin and atorvastatin are used for usual standard therapies. The best statins reduce LDL-C effectively by at least 40%, and also triglycerides, a synergistic risk factor, but less effectively. In contrast, fibrates reduce triglycerides effectively, but not LDL-C. Combination of a statin and a fibrate  
10       proved to be very efficacious in lowering LDL-C and triglycerides (Ellen and McPherson, J. Cardiol. 81, 1998, 60B-65B), but safety of such a combination remains an issue (Shepherd, Eur. Heart J. 16, 1995, 5-13). A single drug with a mixed profile combining effective lowering of both LDL-C and triglycerides would provide additional clinical benefit to asymptomatic and symptomatic patients.

15       In humans, statins are well tolerated at standard dosage, but reductions in non-sterol intermediates in the cholesterol synthesis pathway, such as isoprenoids and coenzyme Q, may be associated with adverse clinical events at high doses (Davignon et al., Can. J. Cardiol. 8, 1992, 843-864; Pederson and Tobert, Drug Safety 14, 1996, 11-24).

20       This has stimulated the search for and development of compounds that inhibit cholesterol biosynthesis, yet act distal to the synthesis of these important, non-sterol intermediates. 2,3-oxidosqualene:lanosterol cyclase (OSC), a microsomal enzyme, represents a unique target for a cholesterol-lowering drug (Morand et al., J. Lipid Res., 38, 1997, 373-390; Mark et al., J. Lipid Res. 37, 1996, 148-158). OSC is downstream of farnesyl-pyrophosphate, beyond the synthesis of isoprenoids and coenzyme Q. In  
25       hamsters, pharmacologically active doses of an OSC inhibitor showed no adverse side-effects, in contrast to a statin which reduced food-intake and body weight, and increased plasma bilirubin, liver weight and liver triglyceride content (Morand et al., J. Lipid Res., 38, 1997, 373-390). The compounds described in European Patent Application No. 636 367, which inhibit OSC and which lower the total cholesterol in plasma, belong to these  
30       substances.

OSC inhibition does not trigger the overexpression of HMGR because of an indirect, negative feed-back regulatory mechanism involving the production of 24(S),25-epoxycholesterol (Peffley et al., Biochem. Pharmacol. 56, 1998, 439-449; Nelson et al., J. Biol. Chem. 256, 1981, 1067-1068; Spencer et al., J. Biol. Chem. 260, 1985, 13391-13394;  
35       Panini et al., J. Lipid Res. 27, 1986, 1190-1204; Ness et al., Arch. Biochem. Biophys. 308, 1994, 420-425). This negative feed-back regulatory mechanism is fundamental to the

- 4 -

concept of OSC inhibition because (i) it potentiates synergistically the primary inhibitory effect with an indirect down-regulation of HMGR, and (ii) it prevents the massive accumulation of the precursor monooxidosqualene in the liver. In addition, 24(S),25-epoxycholesterol was found to be one of the most potent agonists of the nuclear receptor LXR (Janowski et al., Proc. Natl. Acad. Sci. USA, 96, 1999, 266-271). Considering that 24(S),25-epoxycholesterol is a by-product of inhibition of OSC it is hypothesized that the OSC inhibitors of the present invention could also indirectly activate LXR-dependent pathways such as (i) cholesterol-7 $\alpha$ -hydroxylase to increase the consumption of cholesterol via the bile acid route, (ii) expression of ABC1 and/or ABC8 proteins with the potential to stimulate reverse cholesterol transport and increase plasma HDL-C levels (Venkateswaran et al., J. Biol. Chem. 275, 2000, 14700-14707; Costet et al., J. Biol. Chem. June 2000, in press; Ordovas, Nutr Rev 58, 2000, 76-79), and/or inhibit intestinal cholesterol absorption (Mangelsdorf, XIIth International Symposium on Atherosclerosis, Stockholm, June 2000). In addition, possible cross talks between fatty acid and cholesterol metabolism mediated by liver LXR have been hypothesized (Tobin et al., Mol. Endocrinol. 14, 2000, 741-752).

The present compounds of formula I inhibit OSC and therefore also inhibit the cholesterol and ergosterol biosynthesis, and reduce the plasma cholesterol levels. They can therefore be used in the therapy and prophylaxis of hypercholesterolemia, hyperlipemia, arteriosclerosis and vascular diseases in general. Furthermore, they can be used in the therapy and/or prevention of mycoses, gallstones, tumors and hyperproliferative disorders. In addition, it has unexpectedly been found that the compounds of the present invention can also be of therapeutical use to improve glucose tolerance in order to treat and/or prevent related diseases such as diabetes. The compounds of the present invention further exhibit improved pharmacological properties compared to known compounds.

Unless otherwise indicated the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to seven, preferably of one to four carbon atom(s).

The term "lone pair" refers to an unbound electron pair, in particular to the unbound electron pair of a nitrogen atom in e.g. an amine.

The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty

- 5 -

carbon atoms, preferably one to sixteen carbon atoms. Alkyl groups can be substituted e.g. with halogen, particularly with fluorine or chlorine, hydroxy, lower-alkoxy, and/or lower-alkoxy-carbonyl.

5 The term "lower-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like. A lower-alkyl group may have a substitution pattern as described earlier in connection with the term "alkyl".

10 The term "cycloalkyl" refers to a monovalent carbocyclic radical of 3 to 10 carbon atom(s), preferably 3 to 6 carbon atoms. Cycloalkyl in which one or more  $-CH_2-$  group is replaced by O, S, NH or N(lower-alkyl) are referred to as "heterocycloalkyl".

The term "alkoxy" refers to the group  $R'-O-$ , wherein  $R'$  is an alkyl. The term "lower-alkoxy" refers to the group  $R'-O-$ , wherein  $R'$  is a lower-alkyl. The term "thio-alkoxy" refers to the group  $R'-S-$ , wherein  $R'$  is an alkyl. The term "thio-lower-alkoxy" refers to the group  $R'-S-$ , wherein  $R'$  is a lower-alkyl.

20 The term "alkenyl", alone or in combination with other groups, stands for a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 20, preferably up to 16 carbon atoms. The term "lower-alkenyl" refers to a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 7, preferably up to 4 carbon atoms, such as e.g. 2-propenyl. An alkenyl or lower-alkenyl group may have a substitution pattern as described earlier in connection with the term "alkyl".

25 The term "alkinyl", alone or in combination with other groups, stands for a straight-chain or branched hydrocarbon residue comprising a tripple bond and up to 20, preferably up to 16 carbon atoms. The term "lower-alkinyl" refers to a straight-chain or branched hydrocarbon residue comprising a tripple bond and up to 7, preferably up to 4 carbon atoms, such as e.g. 2-propinyl. An alkinyl or lower-alkinyl group may have a substitution pattern as described earlier in connection with the term "alkyl".

30 The term "alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 20 carbon atoms, preferably 1 to 16 carbon atoms. The term "lower-alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 7, preferably 3 to 6 carbon atoms. An alkylene or lower-alkylene group may have a substitution pattern as described earlier in connection with the term "alkyl".

- 6 -

The term "alkenylene" refers to a straight chain or branched divalent hydrocarbon group comprising an olefinic bond and up to 20 carbon atoms, preferably up to 16 carbon atoms. The term "lower-alkenylene" refers to a straight chain or branched divalent hydrocarbon group comprising an olefinic bond and up to 7, preferably up to 6 C-atoms.

- 5 An alkenylene or lower-alkenylene group may have a substitution pattern as described earlier in connection with the term "alkyl".

The term "aryl" relates to the phenyl or naphthyl group which can optionally be mono- or multiply-substituted by lower-alkyl, dioxo-lower-alkylene (forming e.g. a benzodioxyl group), halogen, hydroxy, cyano,  $\text{CF}_3$ ,  $\text{NH}_2$ ,  $\text{N}(\text{lower-alkyl})_2$ , aminocarbonyl, 10 carboxy, nitro, lower-alkoxy, thio-lower-alkoxy, lower-alkylcarbonyl, lower-alkylcarbonyloxy, aryl, or aryloxy. Preferred substituents are lower-alkyl, lower-alkoxy, thio-lower-alkoxy, lower-alkyl-carbonyl, lower-alkoxycarbonyl, fluorine, chlorine, bromine,  $\text{CN}$ ,  $\text{CF}_3$ , and/or dioxo-lower-alkylene. More preferred substituents are fluorine, chlorine, bromine and  $\text{CF}_3$ .

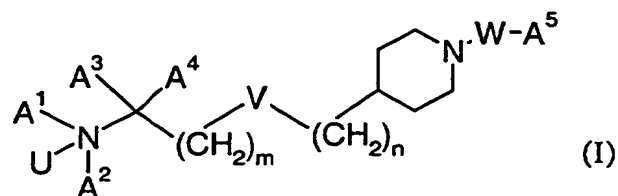
15 The term "heteroaryl" refers to an aromatic 5- or 6-membered ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur such as furyl, pyridyl, 1,2-, 1,3- and 1,4-diazinyl, thienyl, isoxazolyl, oxazolyl, imidazolyl, or pyrrolyl. The term "heteroaryl" further refers to bicyclic aromatic groups comprising two 5- or 6-membered rings, in which one or both rings can contain 1, 2 or 3 atoms selected from 20 nitrogen, oxygen or sulphur such as e.g. indol or chinolin, or partially hydrogenated bicyclic aromatic groups such as e.g. indolinyl. A heteroaryl group may have a substitution pattern as described earlier in connection with the term "aryl".

The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, 25 nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts are formiates, hydrochlorides and hydrobromides.

30 The term "pharmaceutically acceptable esters" embraces esters of the compounds of formula (I), in which hydroxy groups have been converted to the corresponding esters with inorganic or organic acids such as nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms.

- 7 -

In detail, the present invention relates to compounds of formula (I)



wherein

- U is O or a lone pair,
- 5 V is O, -CH<sub>2</sub>-, -CH=CH-, or -C≡C-,
- m and n independently from each other are 0 to 7 and m+n is 0 to 7,
- W is CO, COO, CONR<sup>1</sup>, CSO, CSNR<sup>1</sup>, SO<sub>2</sub>, or SO<sub>2</sub>NR<sup>1</sup>, with the proviso that:
- a) V is not -CH<sub>2</sub>- if W is CO,
- b) m+n is 1 to 2 if V is -CH<sub>2</sub>- and W is SO<sub>2</sub>,
- 10 c) m=n=0 if V is -CH=CH- and W is CO or SO<sub>2</sub>,
- d) m is 1 to 7 if V is O,
- e) n is 1 to 6 or m+n is 1 to 3 if V is O and W is CO or SO<sub>2</sub>,
- A<sup>1</sup> is H, lower-alkyl or lower-alkenyl,
- A<sup>2</sup> is cycloalkyl, cycloalkyl-lower-alkyl, lower-alkenyl, lower alkynyl, or lower-alkyl
- 15 optionally substituted with hydroxy, lower-alkoxy or lower-alkoxy-carbonyl,
- A<sup>3</sup> and A<sup>4</sup> are hydrogen or lower-alkyl, or
- A<sup>1</sup> and A<sup>2</sup> or A<sup>1</sup> and A<sup>3</sup> are bonded to each other to form a ring
- and -A<sup>1</sup>-A<sup>2</sup>- or -A<sup>1</sup>-A<sup>3</sup>- are lower-alkylene or lower-alkenylene, optionally
- substituted by R<sup>2</sup>, in which one -CH<sub>2</sub>- group of -A<sup>1</sup>-A<sup>2</sup>- or -A<sup>1</sup>-A<sup>3</sup>- can
- 20 optionally be replaced by NR<sup>3</sup>, S, or O,
- A<sup>5</sup> is lower-alkyl optionally substituted with halogen, lower-alkenyl, lower-alkoxy-carbonyl-lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, or heteroaryl-lower-alkyl,
- R<sup>2</sup> is lower-alkyl, hydroxy, hydroxy-lower-alkyl, or N(R<sup>4</sup>,R<sup>5</sup>),
- 25 R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> independently from each other are hydrogen or lower-alkyl,
- and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

- 8 -

Preferred are compounds of formula (I) and/or pharmaceutically acceptable salts thereof. Other preferred embodiments relate to compounds of formula (I) wherein U is a lone pair or to compounds of formula (I) wherein U is O. Compounds as described above in which V is O relate to a further preferred embodiment of the present invention.

- 5        Of the compounds of the present invention, those in which W represents CO, COO, CONR<sup>1</sup>, SO<sub>2</sub> or SO<sub>2</sub>NR<sup>1</sup> and R<sup>1</sup> is hydrogen are preferred, with those wherein W represents CO, COO or SO<sub>2</sub>NR<sup>1</sup> and R<sup>1</sup> is hydrogen being particularly preferred.

- Compounds of the present invention in which n is 0 to 2 are preferred, with those wherein n is 1 to 2 being particularly preferred. Another preferred embodiment relates to  
10       compounds as defined above, wherein m is 1 to 5.

- Other preferred compounds of the present invention are those in which A<sup>1</sup> represents methyl, ethyl, or 2-propenyl. Another group of preferred compounds of the present invention are those in which A<sup>2</sup> represents methyl, n-propyl, i-propyl, n-butyl, 2-propenyl, 2-propinyl, cyclopropyl, cyclohexyl, cyclopropyl-methylene, or ethyl optionally  
15       substituted with hydroxy, methoxy, or ethoxycarbonyl, with those compounds wherein A<sup>2</sup> represents 2-hydroxy-ethyl, 2-propenyl, or cyclopropyl being especially preferred.

- Compounds of formula (I), wherein A<sup>1</sup> and A<sup>2</sup> are bonded to each other to form a ring and -A<sup>1</sup>-A<sup>2</sup>- is lower-alkylene, or lower-alkenylene, optionally substituted by R<sup>2</sup>, in which one -CH<sub>2</sub>- group of -A<sup>1</sup>-A<sup>2</sup>- can optionally be replaced by NR<sup>3</sup>, S, or O, wherein R<sup>2</sup>  
20       is lower-alkyl, hydroxy, hydroxy-lower-alkyl, or N(lower-alkyl)<sub>2</sub>, and R<sup>3</sup> is lower alkyl are also preferred, with those compounds wherein said optional substituent R<sup>2</sup> is methyl, hydroxy, 2-hydroxyethyl, or N(CH<sub>3</sub>)<sub>2</sub> and R<sub>3</sub> is methyl being particularly preferred. In compounds wherein A<sup>1</sup> and A<sup>2</sup> are bonded to each other to form a ring, said ring is preferably a 4-, 5-, or 6-membered ring such as e.g. piperidinyl or pyrrolidinyl.

- 25       A further preferred embodiment of the present invention relates to compounds of formula (I), wherein A<sup>3</sup> and/or A<sup>4</sup> represent hydrogen.

- Compounds of formula (I), wherein A<sup>5</sup> as defined above is not heteroaryl or wherein A<sup>5</sup> is lower-alkyl optionally substituted by one or more substituents selected from the group consisting of fluorine and chlorine, lower-alkenyl, cycloalkyl, cycloalkyl-lower-alkyl,  
30       lower-alkoxy-carbonyl-lower-alkyl, naphthyl, furyl-methylene, or phenyl, benzyl or phenyl-ethylene, optionally substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, CN, CF<sub>3</sub>, NO<sub>2</sub>, lower-alkyl, lower-alkoxy, thio-lower-alkoxy, lower-alkyl-carbonyl, lower-alkoxy-carbonyl, and dioxo-lower-alkylene are other preferred embodiments of the present invention, with those compounds wherein  
35       A<sup>5</sup> is lower-alkyl, cycloalkyl-lower-alkyl, or phenyl or benzyl optionally substituted by one



- 9 -

or more substituents selected from the group consisting of fluorine, chlorine, bromine, and CF<sub>3</sub> being more preferred, and with those compounds wherein wherein A<sup>5</sup> is n-butyl, i-butyl, cyclohexyl-methylene, phenyl, 4-chloro-phenyl, 4-bromo-phenyl, 2,5-difluoro-phenyl, 3,4-difluoro-phenyl, 4-trifluoromethyl-phenyl, or 4-chloro-benzyl being  
 5 particularly preferred.

Further preferred embodiments of the present invention are those compounds as defined above wherein V is not -CH<sub>2</sub>- or -CH=CH- if W is CO or SO<sub>2</sub>, or wherein W is not CO and/or SO<sub>2</sub> at all.

Preferred compounds of general formula (I) are those selected from the group  
 10 consisting of  
 {4-[4-(Allyl-methyl-amino)-butoxy]-piperidin-1-yl}-(4-bromo-phenyl)-methanone,  
 {4-[3-(Allyl-methyl-amino)-propoxy]-piperidin-1-yl}-(4-bromo-phenyl)-methanone,  
 Allyl-{4-[1-(4-chloro-benzenesulfonyl)-piperidin-4-yloxy]-butyl}-methyl-amine,  
 Allyl-{4-[1-(4-bromo-benzenesulfonyl)-piperidin-4-yloxy]-butyl}-methyl-amine,  
 15 Allyl-{3-[1-(4-bromo-benzenesulfonyl)-piperidin-4-yloxy]-propyl}-methyl-amine,  
 1-{4-[5-(Allyl-methyl-amino)-pentyloxy]-piperidin-1-yl}-2-(4-fluoro-phenyl)-ethanone,  
 1-{4-(5-Diethylamino-pentyloxy)-piperidin-1-yl}-2-(4-fluoro-phenyl)-ethanone,  
 2-(4-Fluoro-phenyl)-1-(4-{5-[(2-methoxy-ethyl)-methyl-amino]-pentyloxy}-piperidin-1-yl)-ethanone,  
 20 1-{4-[5-(Cyclopropyl-methyl-amino)-pentyloxy]-piperidin-1-yl}-2-(4-fluoro-phenyl)-ethanone,  
 1-{4-[4-(Allyl-methyl-amino)-butoxy]-piperidin-1-yl}-2-(4-chloro-phenyl)-ethanone,  
 2-(4-Chloro-phenyl)-1-(4-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-piperidin-1-yl)-ethanone,  
 25 {4-[4-(Allyl-methyl-amino)-butoxy]-piperidin-1-yl}-(4-chloro-phenyl)-methanone,  
 (4-Chloro-phenyl)-(4-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-piperidin-1-yl)-methanone,  
 4-[4-(Allyl-methyl-amino)-butoxy]-piperidine-1-carboxylic acid 4-chloro-phenyl ester,  
 4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-piperidine-1-carboxylic acid 4-chloro-phenyl ester,  
 30 4-[4-(Allyl-methyl-amino)-butoxy]-piperidine-1-carboxylic acid isobutyl ester,  
 4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-piperidine-1-carboxylic acid isobutyl ester,  
 1-(4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-ethanone,  
 35 2-(4-Chloro-phenyl)-1-[4-(2-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-ethyl)-piperidin-1-yl]-ethanone,

- 10 -

- (4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidin-1-yl)-(4-chloro-phenyl)-methanone,
- (4-Chloro-phenyl)-[4-(2-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-ethyl)-piperidin-1-yl]-methanone,
- 5 4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidine-1-carboxylic acid 4-chloro-phenyl ester,
- 4-(2-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-ethyl)-piperidine-1-carboxylic acid 4-chloro-phenyl ester,
- 4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidine-1-carboxylic acid isobutyl ester,
- 10 4-(2-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-ethyl)-piperidine-1-carboxylic acid isobutyl ester,
- 1-(4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-ethanone,
- 2-(4-Chloro-phenyl)-1-[4-(2-{2-[ethyl-(2-hydroxy-ethyl)-amino]-ethoxy}-ethyl)-piperidin-1-yl]-ethanone,
- 15 (4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidin-1-yl)-(4-chloro-phenyl)-methanone,
- (4-Chloro-phenyl)-[4-(2-{2-[ethyl-(2-hydroxy-ethyl)-amino]-ethoxy}-ethyl)-piperidin-1-yl]-methanone,
- 20 4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidine-1-carboxylic acid 4-chloro-phenyl ester,
- 4-(2-{2-[Ethyl-(2-hydroxy-ethyl)-amino]-ethoxy}-ethyl)-piperidine-1-carboxylic acid 4-chloro-phenyl ester,
- 4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidine-1-carboxylic acid isobutyl ester,
- 25 4-(2-{2-[Ethyl-(2-hydroxy-ethyl)-amino]-ethoxy}-ethyl)-piperidine-1-carboxylic acid isobutyl ester,
- 1-(4-{2-[3-(Allyl-methyl-amino)-propoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-ethanone,
- 2-(4-Chloro-phenyl)-1-[4-(2-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-ethyl)-piperidin-1-yl]-ethanone,
- 30 (4-{2-[3-(Allyl-methyl-amino)-propoxy]-ethyl}-piperidin-1-yl)-(4-chloro-phenyl)-methanone,
- (4-Chloro-phenyl)-[4-(2-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-ethyl)-piperidin-1-yl]-methanone,
- 35 4-{2-[3-(Allyl-methyl-amino)-propoxy]-ethyl}-piperidine-1-carboxylic acid 4-chloro-phenyl ester,
- 4-(2-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-ethyl)-piperidine-1-carboxylic acid 4-chloro-phenyl ester,
- 2-(4-Chloro-phenyl)-1-(4-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxymethyl}-piperidin-

- 11 -

- 1-yl)-ethanone,  
 1-{4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidin-1-yl}-2-(4-chloro-phenyl)-  
 ethanone,  
 {4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidin-1-yl}-(4-chloro-phenyl)-  
 5 methanone,  
 (4-Chloro-phenyl)-(4-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxymethyl}-piperidin-1-  
 yl)-methanone,  
 1-{4-[3-(Allyl-methyl-amino)-propoxymethyl]-piperidin-1-yl}-2-(4-chloro-phenyl)-  
 ethanone,  
 10 2-(4-Chloro-phenyl)-1-(4-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-  
 piperidin-1-yl)-ethanone,  
 {4-[3-(Allyl-methyl-amino)-propoxymethyl]-piperidin-1-yl}-(4-chloro-phenyl)-  
 methanone,  
 (4-Chloro-phenyl)-(4-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-piperidin-1-  
 15 yl)-methanone,  
 4-[3-(Allyl-methyl-amino)-propoxymethyl]-piperidine-1-carboxylic acid 4-chloro-phenyl  
 ester,  
 4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-piperidine-1-carboxylic acid 4-  
 chloro-phenyl ester,  
 20 4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidine-1-carboxylic acid 4-chloro-phenyl  
 ester,  
 4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxymethyl}-piperidine-1-carboxylic acid 4-  
 chloro-phenyl ester,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-fluoro-3-  
 25 trifluoromethyl-phenyl)-amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (2,4-difluoro-phenyl)-  
 amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (2,4-dimethoxy-  
 phenyl)-amide,  
 30 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-fluoro-phenyl)-  
 amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-methoxy-phenyl)-  
 amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid p-tolylamide,  
 35 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-methoxy-2-methyl-  
 phenyl)-amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (2,4-dimethyl-phenyl)-  
 amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (3,4,5-trimethoxy-

- phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (3,4-dimethyl-phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-acetyl-phenyl)-amide,  
5 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-butyl-phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-methylsulfanyl-phenyl)-amide,  
10 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-isopropyl-phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (3,4-dichloro-phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-bromo-phenyl)-amide,  
15 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid naphthalen-2-ylamide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid naphthalen-1-ylamide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid phenethyl-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid ethyl ester,  
20 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid methyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester,  
25 4-[6-(allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-nitro-phenyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid isobutyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid benzyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid allyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid phenyl ester,  
30 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid butyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-methoxycarbonyl-phenyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-fluoro-phenylester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-bromo-phenyl ester,  
35 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-chloro-phenyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid p-tolyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-trifluoromethyl-phenyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid benzylamide,

- 13 -

- 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid butylamide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenethyl-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (furan-2-ylmethyl)-  
amide,  
5 {4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonylamino}-acetic acid ethyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid cyclohexylmethyl-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid cyclopropylamide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,2,2-trifluoro-ethyl)-  
amide,  
10 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (benzo[1,3]dioxol-5-  
ylmethyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid 4-fluoro-benzylamide,  
4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-chloro-  
phenyl)-amide,  
15 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-chloro-phenyl)-  
amide,  
4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-fluoro-  
phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-fluoro-phenyl)-amide,  
20 4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-bromo-  
phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-bromo-phenyl)-  
amide,  
4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (p-tolyl)-amide,  
25 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (p-tolyl)-amide,  
4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3,4-difluoro-  
phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3,4-difluoro-phenyl)-  
amide,  
30 4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-  
trifluoromethyl-phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-trifluoromethyl-  
phenyl)-amide,  
4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3-fluoro-  
35 phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3-fluoro-phenyl)-amide,  
4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-cyano-  
phenyl)-amide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-cyano-phenyl)-amide,

- 14 -

- 4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,4-difluoro-phenyl)-amide,
- 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,4-difluoro-phenyl)-amide,
- 5 4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-methoxy-phenyl)-amide,
- 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-methoxy-phenyl)-amide,
- 4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,5-difluoro-phenyl)-amide,
- 10 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,5-difluoro-phenyl)-amide,
- 4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (phenyl)-amide,
- 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (phenyl)-amide,
- 15 4-(6-Azepan-1-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide,
- 4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-piperidine-1-sulfonic acid phenylamide,
- 4-[6-(Ethyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,
- 4-[6-(2-Methyl-piperidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,
- 20 4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-piperidine-1-sulfonic acid phenylamide,
- {Methyl-[6-(1-phenylsulfamoyl-piperidin-4-yloxy)-hexyl]-amino}-acetic acid ethyl ester,
- 4-[6-(Butyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,
- 4-(6-Diallylamino-hexyloxy)-piperidine-1-sulfonic acid phenylamide,
- 25 4-(6-Pyrrolidin-1-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide,
- 4-[6-(Methyl-prop-2-ynyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,
- 4-(6-Piperidin-1-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide,
- 4-[6-(Ethyl-isopropyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,
- 4-(6-Morpholin-4-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide,
- 30 4-[6-(Isopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,
- 4-[6-(3,6-Dihydro-2H-pyridin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,
- 4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-piperidine-1-sulfonic acid phenylamide,
- 4-(6-Dimethylamino-hexyloxy)-piperidine-1-sulfonic acid phenylamide,
- 4-[6-(Methyl-propyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,
- 35 4-(6-Diethylamino-hexyloxy)-piperidine-1-sulfonic acid phenylamide,
- 4-(6-Thiomorpholin-4-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide,
- 4-[6-(Butyl-ethyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,
- 4-(6-Thiazolidin-3-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide,
- 4-[6-(4-Hydroxy-piperidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,

- 15 -

- 4-[6-(4-Methyl-piperazin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,  
 4-[6-(4-Hydroxymethyl-piperidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid  
 phenylamide,  
 4-[6-(Cyclopropylmethyl-propyl-amino)-hexyloxy]-piperidine-1-sulfonic acid  
 5 phenylamide,  
 4-[6-(3-Hydroxy-piperidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,  
 4-[6-(Cyclohexyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide,  
 4-[6-(3-Dimethylamino-pyrrolidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid  
 phenylamide,  
 10 4-(6-Azetidin-1-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide, and  
 4-[6-(Cyclopropylmethyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid  
 phenylamide,  
 and pharmaceutically acceptable salts thereof.

- Particularly preferred compounds of general formula (I) are those selected from the  
 15 group consisting of  
 Allyl-{4-[1-(4-chloro-benzenesulfonyl)-piperidin-4-yloxy]-butyl}-methyl-amine,  
 Allyl-{3-[1-(4-bromo-benzenesulfonyl)-piperidin-4-yloxy]-propyl}-methyl-amine,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid isobutyl ester,  
 {4-[4-(Allyl-methyl-amino)-butoxy]-piperidin-1-yl}-(4-chloro-phenyl)-methanone,  
 20 1-(4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-  
 ethanone,  
 (4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidin-1-yl)-(4-chloro-phenyl)-  
 methanone,  
 (4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidin-1-yl)-(4-chloro-phenyl)-  
 25 methanone,  
 {4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidin-1-yl}-(4-chloro-phenyl)-  
 methanone,  
 {4-[3-(Allyl-methyl-amino)-propoxymethyl]-piperidin-1-yl}-(4-chloro-phenyl)-  
 methanone,  
 30 4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-piperidine-1-carboxylic acid 4-  
 chloro-phenyl ester,  
 4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidine-1-carboxylic acid 4-chloro-phenyl  
 ester,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid butylamide,  
 35 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid cyclohexylmethyl-amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-chloro-phenyl)-  
 amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-bromo-phenyl)-

- 16 -

amide,

4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3,4-difluoro-phenyl)-amide,

4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-trifluoromethyl-phenyl)-amide,

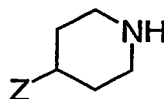
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,5-difluoro-phenyl)-amide, and

4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (phenyl)-amide, and pharmaceutically acceptable salts thereof.

Compounds of formula (I) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers or as racemats. The invention embraces all of these forms.

It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

The present invention also relates to a process for the manufacture of compounds as described above, which process comprises reacting a compound of formula (II)



(II)

wherein Z is  $(A^1, A^2)N-C(A^3, A^4)-(CH_2)_m-V-(CH_2)_n$ ,  $X-CH_2-(CH_2)_m-V-(CH_2)_n$ ,  $HO(CH_2)_n$ , or  $HOOC(CH_2)_n$ , wherein X is chlorine, bromine, iodine, methanesulfonyl, or toluenesulfonyl, and  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ , V, m and n are as defined above,

with  $ClSO_2-A^5$ ,  $ClCOO-A^5$ ,  $ClCSO-A^5$ ,  $OCN-A^5$ ,  $SCN-A^5$ ,  $HOOC-A^5$ , or  $ClSO_2NR^1-A^5$ , wherein  $A^5$  is as defined above.

The invention further relates to compounds of formula (I) as defined above, when manufactured according to a process as defined above.

As described above, the compounds of formula (I) of the present invention can be used for the treatment and/or prophylaxis of diseases which are associated with OSC such as of hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses and gallstones, and/or treatment and/or prophylaxis of impaired glucose tolerance, diabetes, tumors and/or hyperproliferative disorders.



- 17 -

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, which method comprises administering a compound as defined above to a human being or animal.

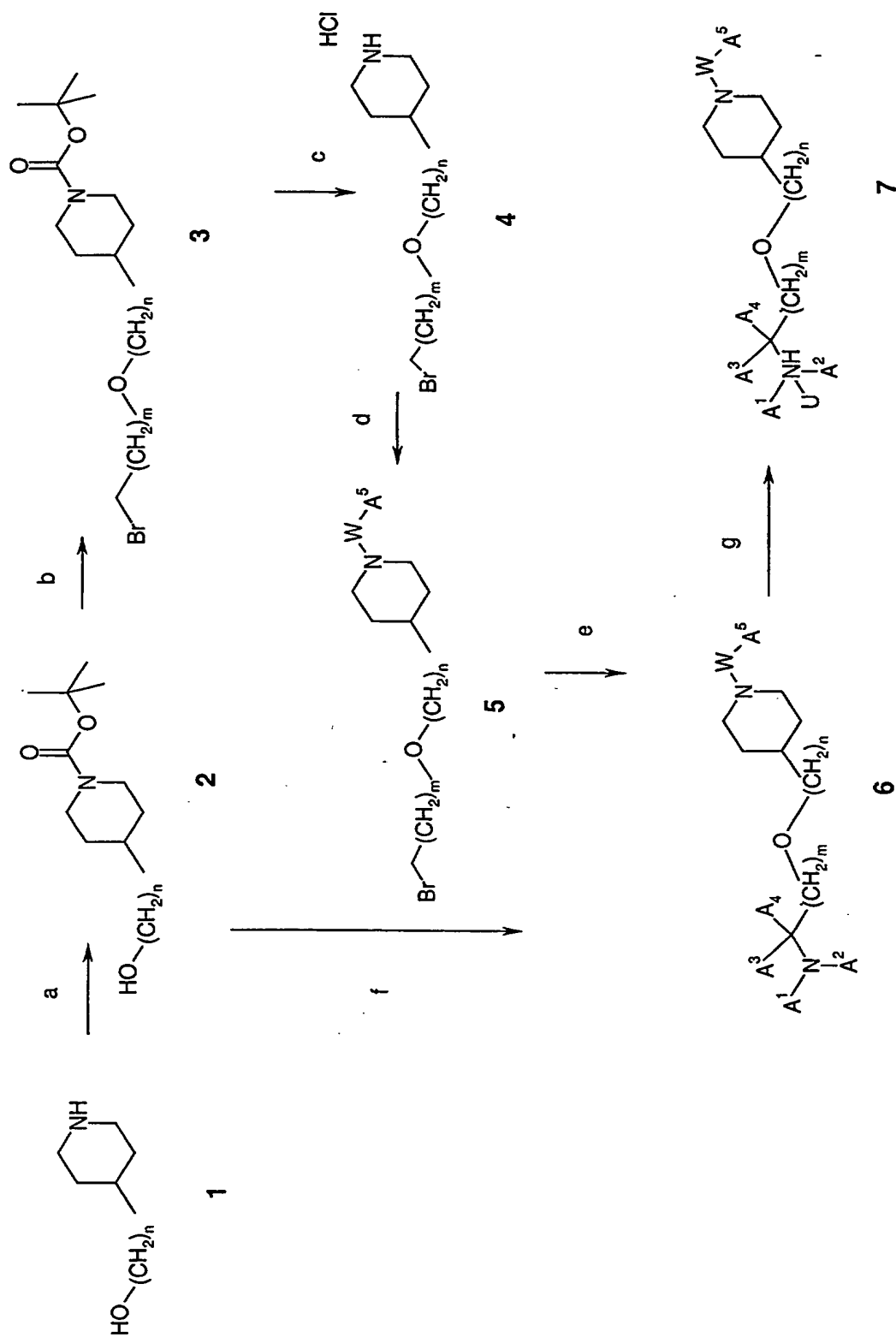
The invention further relates to the use of compounds as defined above for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes. Such medicaments comprise a compound as defined above.

The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to the person skilled in the art. Starting materials are either commercially available or can be prepared by methods analogous to the methods given in the examples or by methods known in the art.

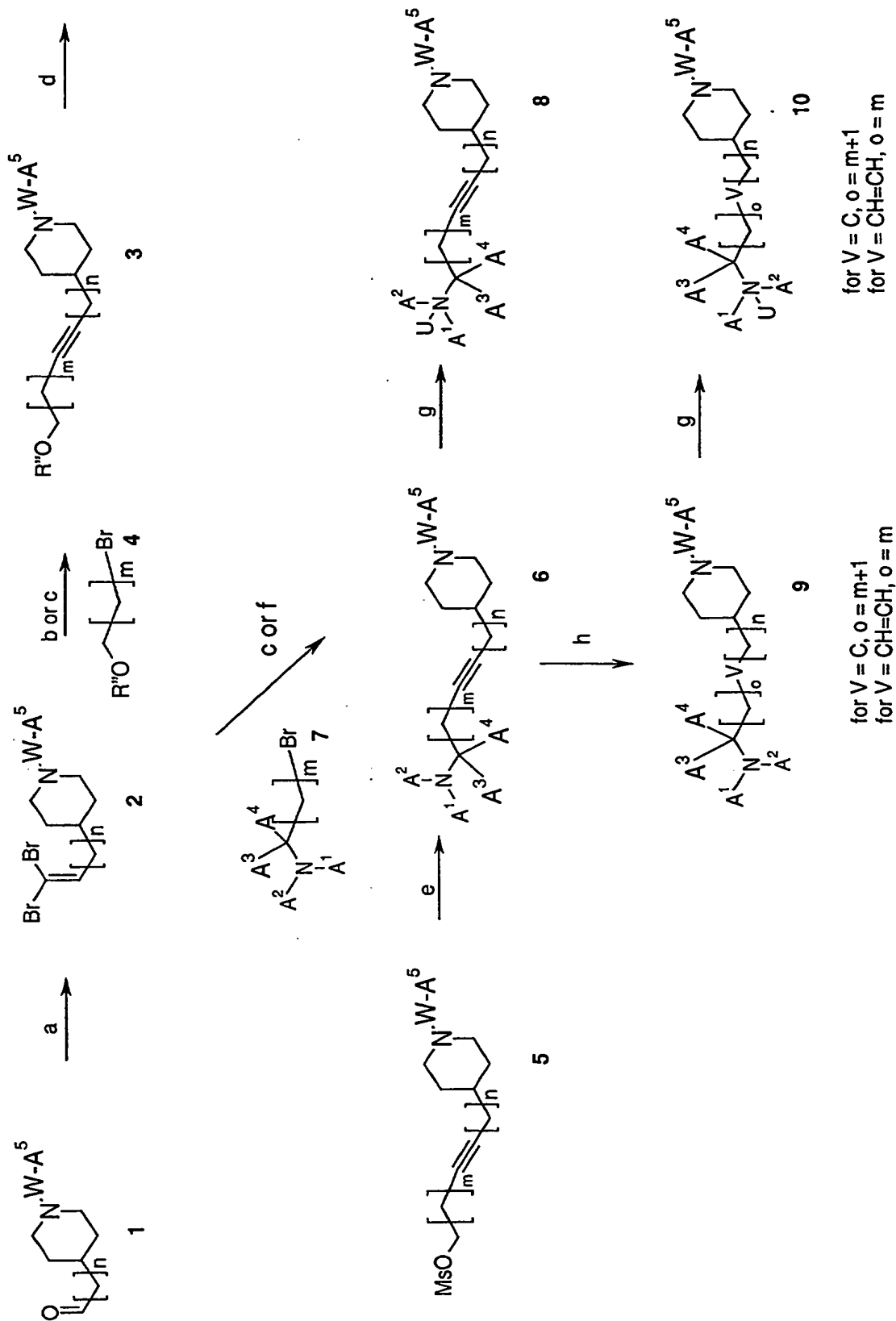
- 18 -

Scheme 1



- 19 -

Scheme 2



## Scheme 1:

In Scheme 1, an overview of the synthesis of the compounds of the present invention is shown. Hydroxypiperidine 1 or hydroxyalkylpiperidine 1 is N-BOC-protected (step a) in  $\text{CH}_2\text{Cl}_2$  with di-tert-butyl dicarbonate at RT. O-Alkylation of the N-BOC-protected piperidene 2 (step b) in DMF with NaH as base and dihaloalkane, dihaloalkene, (halogene is here represented by bromine, but can be also, Cl, I, mesylate or tosylate) at 0 °C to RT yields halogenide 3. For shorter alkanes ( $\text{C}_2$ - and  $\text{C}_3$ -alkanes) the method of choice is the in situ generation of the haloalkane-triflate (from the corresponding haloalkanol with trifluoromethanesulfonic anhydride/2,6-di-tert-butylpyridine in  $\text{CH}_2\text{Cl}_2$  at 0 °C). This haloalkane-triflate is then reacted with alcohol 2 with 2,6-di-tert-butylpyridine as base in nitromethane at 60 °C to yield bromide 3 [following a procedure of Belostotskii, Anatoly M.; Hassner, Alfred. Synthetic methods. 41. Etherification of hydroxysteroids via triflates. Tetrahedron Lett. (1994), 35(28), 5075-6].

Boc deprotection (step c) in  $\text{CH}_2\text{Cl}_2$  at RT with 4N HCl in dioxane yields hydrochloride 4. This building block is then further transformed to intermediate 5 by one of the following procedures:

- 1) Sulfonylation of compound 4 is done in dioxane with Hünigbase and a sulfonyl chloride over night at RT to yield the sulfonamide 5.
- 2) Compound 4 may be reacted with  $\text{A}^5\text{OCOCl}$ /Hünigbase in dioxane or  $\text{CH}_2\text{Cl}_2$  or by reaction of  $\text{A}^5\text{OH}/\text{Cl}_3\text{COCl}$ /quinoline (formation of the chloroformate) followed by reaction with compound 4 and Hünigbase to yield the corresponding carbamate.
- 3) Compound 4 may be reacted with  $\text{A}^5\text{OCSCl}$  in dioxane to yield the corresponding thiocarbamate.
- 4) Compound 4 may be reacted with an isocyanate in dioxane at room temperature to yield the corresponding urea.
- 5) Compound 4 may be reacted with an isothiocyanate in dioxane at room temperature to yield the corresponding thiourea.
- 6) Compound 4 may be reacted with  $\text{A}^5\text{COCl}$ /Hünigbase in  $\text{CH}_2\text{Cl}_2$ , or with  $\text{A}^5\text{COOH}$ /EDCI/DMAP (anhydride formation and subsequent addition of the amine, -10 °C to room temperature) or as alternative with  $\text{A}^5\text{COOH}$ /EDCI/DMAP or  $\text{A}^5\text{COOH}$ /Hünigbase/EDCI/HOBT in DMF, dioxane or  $\text{CH}_2\text{Cl}_2$  at room temperature to yield the corresponding amide.

- 21 -

- 7) Compound 4 may be reacted with a sulfamoyl chloride in dioxane in the presence of an excess of triethylamine to yield the corresponding sulfamide 5. The sulfamoyl chlorides were synthesized from  $A^5NH_2$  and chlorosulfonic acid in  $CH_2Cl_2$  at 0 °C to room temperature followed by reaction with  $PCl_5$  in toluene at 75 °C. Alternatively the sulfamoyl chlorides can be synthesized in acetonitrile with  $A^5NH_2$  and sulfonyl chloride at 0 °C to 65 °C.

These compounds 5 are then converted (step e) to the amine 6 in DMA at RT with an excess of the corresponding amine  $A^1A^2NH$  or in acetone with  $K_2CO_3$  at 65 °C.

- Alternatively, the mesylate or halogenide of the group  $A^1A^2NC(A^3A^4)-(CH_2)-$  can be synthesized by known methods and attached to building block 2 (NaH in DMF), to yield directly amine 6 (step f).

The amines 6 can optionally be converted to a salt or to the N-oxide 7 (compound 6 was reacted with a mixture of hydrogen peroxide adduct and phthalic anhydride in  $CH_2Cl_2$  at RT, step g).

#### 15 Scheme 2:

- In scheme 2 the synthesis of compounds of the general formula (I) in which V is -  $CH_2-$ , - $CH=CH-$  or - $C\equiv C-$  is described. The synthesis starts from aldehyde 1 which can be derived from a suitable protected 4-piperidinecarboxylic acid (such as BOC-4-piperidinecarboxylic acid or  $WA^5$ -4-piperidinecarboxylic acid, via Weinreb-amide and LAH reduction) or from the corresponding alcohol by Swern oxidation. Side chain extension is effected through application of the Corey-Fuchs method. The aldehyde 1 is treated with triphenylphosphine, tetra-bromo-methane and triethylamine in  $CH_2Cl_2$  at 0 °C to RT to yield 2,2-Dibromo-vinyl derivative 2 (step a). Rearrangement with *n*-BuLi (ca 1.6 M in hexane) in THF at -78 °C, followed by reaction with formaldehyde (-78 °C to RT) leads to the propargyl alcohol 3 [step b, following conditions described in: Marshall, James A.; Bartley, Gary S.; Wallace, Eli M. Total Synthesis of the Pseudopterane (-)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B. J. Org. Chem. (1996), 61(17), 5729-5735; and Baker, Raymond; Boyes, Alastair L.; Swain, Christopher J. Synthesis of talaromycins A, B, C, and E., J. Chem. Soc., Perkin Trans. 1 (1990), (5), 1415-21.].

- For longer side chains, the rearrangement is performed with *n*-BuLi (ca 1.6 M in hexane) in THF at -78 °C as above, followed by addition of a cosolvent such as DMPU and reaction with O-protected 1-bromo-alcohols 4 (e.g. 1-bromo-*n*-tetrahydro-pyranyloxyalkane) to yield the O-protected compounds 3 (step c) which can be

- 22 -

deprotected to the corresponding alkinol derivative (in MeOH at 50-60 °C in the presence of catalytic amount of pyridinium toluene-4-sulfonate).

Mesylation of the resulting alcohol with methanesulfonylchloride, pyridine and DMAP in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C to RT yields mesylate 5 (step d) which can be converted to the  
5 amine 6 in DMA at RT with an excess of the corresponding amine NHA<sup>1</sup>A<sup>2</sup> (step e).

If A<sup>5</sup>W is a protecting moiety this can be cleaved prior to salt or n-oxide formation using TFA in CH<sub>2</sub>Cl<sub>2</sub> for BOC-groups or by hydrogenation in methanol with Pd/C for Z-groups. The resulting amine (not shown) may be treated according to one of the procedures described for scheme 1 to yield a derivative 6 with a desired A<sup>5</sup>W group.

10 Optionally, the introduction of the desired A<sup>5</sup>W moiety can be performed at an earlier stage, e.g. at the derivative 2 or mesylated compound 5.

To obtain compounds 6 in which A<sup>3</sup> and/or A<sup>4</sup> is not H and m>0, compounds 2 can be reacted with compounds 7 under the same condition as described for step c. The building blocks 7 can be prepared by known methods. For the introduction of the group  
15 (A<sup>1</sup>,A<sup>2</sup>)N-C(A<sup>3</sup>,A<sup>4</sup>)- wherein A<sup>3</sup> and/or A<sup>4</sup> is not H and m=0, a two step procedure has to be followed: first the rearrangement with n-BuLi (ca 1.6 M in hexane) in THF at -78 °C, followed by reaction with the corresponding aldehyde (A<sup>3</sup> or A<sup>4</sup>-COH) or ketone (A<sup>3</sup>COA<sup>4</sup>, at -78 °C to RT) leading to the A<sup>3</sup>,A<sup>4</sup> substituted propargyl alcohol which can be mesylated and reacted with the desired (A<sup>1</sup>,A<sup>2</sup>)-amine to yield the desired A<sup>3</sup>A<sup>4</sup>-substituted  
20 compound 6.

Compounds in which V is -CH<sub>2</sub>- or -CH=CH- can be obtained by hydrogenation of compound 6 with Pt/C (yields the saturated analogue 9) or by hydrogenation with other known methods (yields the double bond analogue 9).

The amines 6 and 9 can be converted to a salt or as described in step f to the N-oxide  
25 8 and 10, respectively, using a mixture of hydrogen peroxide urea adduct and phthalic anhydride in CH<sub>2</sub>Cl<sub>2</sub> at RT.

- 23 -

The following tests were carried out in order to determine the activity of the compounds of formula I and their salts.

Inhibition of human liver microsomal 2,3-oxidosqualene-lanosterol cyclase (OSC)

Liver microsomes from a healthy volunteer were prepared in sodium phosphate buffer (pH 7.4). The OSC activity was measured in the same buffer, which also contained 1mM EDTA and 1mM dithiothreitol. The microsomes were diluted to 0.8mg/ml protein in cold phosphate buffer. Dry [ $^{14}$ C]R,S-monooxidosqualene (MOS, 12.8 mCi/mmol) was diluted to 20 nCi/ $\mu$ l with ethanol and mixed with phosphate buffer-1% BSA (bovine serum albumin). A stock solution of 1 mM test substance in DMSO was diluted to the  
5  
10  
desired concentration with phosphate buffer-1% BSA. 40  $\mu$ l of microsomes were mixed with 20  $\mu$ l of the solution of the test substance and the reaction was subsequently started with 20  $\mu$ l of the [ $^{14}$ C]R,S-MOS solution. The final conditions were: 0.4mg/ml of microsomal proteins and 30  $\mu$ l of [ $^{14}$ C]R,S-MOS in phosphate buffer, pH 7.4, containing 0.5% albumin, DMSO <0.1% and ethanol <2%, in a total volume of 80  $\mu$ l.

15  
After 1 hour at 37°C the reaction was stopped by the addition of 0.6 ml of 10% KOH-methanol, 0.7ml of water and 0.1ml of hexane:ether (1:1, v/v) which contained 25  $\mu$ g of non-radioactive MOS and 25  $\mu$ g of lanosterol as carriers. After shaking, 1 ml of hexane:ether (1:1, v/v) was added to each test tube, these were again shaken and then  
20  
centrifuged. The upper phase was transferred into a glass test tube, the lower phase was again extracted with hexane:ether and combined with the first extract. The entire extract was evaporated to dryness with nitrogen, the residue was suspended in 50  $\mu$ l of hexane:ether and applied to a silica gel plate. Chromatographic separation was effected in hexane:ether (1:1, v/v) as the eluent. The R<sub>f</sub> values for the MOS substrate and the  
25  
lanosterol product were 0.91 and, respectively, 0.54. After drying, radioactive MOS and lanosterol were observed on the silica gel plate. The ratio of MOS to lanosterol was determined from the radioactive bands in order to determine the yield of the reaction and OSC inhibition.

The test was carried out on the one hand with a constant test substance concentration of 100nM and the percentage OSC inhibition against controls was  
30  
calculated. The more preferred compounds of the present invention exhibit inhibitions larger than 50%. In addition, the test was carried out with different test substance concentrations and subsequently the IC<sub>50</sub> value was calculated, i.e. the concentration required to reduce the conversion of MOS into lanosterol to 50% of the control value. The preferred compounds of the present invention exhibit IC<sub>50</sub> values of 1 nM to 10  $\mu$ M,  
35  
preferably of 1 - 100 nM.

- 24 -

The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration for the prevention and



- 25 -

control of topical and systemic infections by pathogenic fungi. For cholesterol lowering and treatment of impaired glucose tolerance and diabetes the daily dosage conveniently amounts to between 1 and 1000mg, preferably 10 to 100mg, for adult patients. Depending on the dosage it is convenient to administer the daily dosage in several dosage units.

- 5       The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 10-100 mg, of a compound of formula I.

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

- 26 -

Examples

## Abbreviations:

- AcOH = acetic acid, EtOAc = ethylacetate, EtOH = ethanol, THF = tetrahydrofurane, Et<sub>2</sub>O = diethylether, MeOH = methanol, CH<sub>2</sub>Cl<sub>2</sub> = dichloromethane, BOC = t-
- 5 butyloxycarbonyl, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene(1,5-5), DMA = N,N-dimethylacetamide, DMAP = 4-Dimethylaminopyridine, EDCI = N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, Et<sub>3</sub>N = triethylamine, HOBT = 1-Hydroxybenzo-triazole, LAH = Lithium aluminium hydride, LDA = lithium diisopropylamide, PdCl<sub>2</sub>(dppf) = (1,1'-bis(diphenylphosphino)ferrocene)-
- 10 dichloropalladium(II).CH<sub>2</sub>Cl<sub>2</sub> (1:1), Pd(Ph<sub>3</sub>P)<sub>4</sub> = tetrakis(triphenylphosphine)palladium, iPr<sub>2</sub>NEt = DIPEA = Huenigsbase = N-ethyldiisopropylamine, TFA = trifluoroacetic acid.

## General remarks

All reactions were performed under argon.

- 15 The purification of the final amines by preparative HPLC [e.g. RP-18; acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile] yielded mixtures of the corresponding amino formate and the corresponding halogenide which was used in the reaction. The ratio was not always determined, the purity of the final amino salts was >80% after LC-MS.

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- 27 -

**Example 1****1.1**

To a solution of 3 g (29.66 mmol) 4-Hydroxypiperidine in 30 ml of  $\text{CH}_2\text{Cl}_2$  was added 7.12 g (32.6 mmol) Di-tert-butyl dicarbonate. The solution was stirred at RT for 2h, 5 diluted with  $\text{Et}_2\text{O}$  and the organic phase was washed with 1N HCl and water. The organic phase was concentrated in vacuo to yield 6.47 g (95 %) 4-Hydroxy-piperidine-1-carboxylic-acid tert-butyl ester.

**1.2a**

To a solution of 10 g (49.7 mmol) 4-Hydroxy-piperidine-1-carboxylic-acid tert-butyl ester 10 and 18 ml (149 mmol) of 1,4-dibromobutane in 100 ml DMF was added under ice-cooling at  $0^\circ\text{C}$ , 3.25 g (74.53 mmol) NaH (57% in oil). After 2h stirring at r.t., 140 ml of sat.  $\text{NH}_4\text{Cl}$ -solution was added carefully. The reaction-mixture was diluted with  $\text{Et}_2\text{O}$  and washed with water. The organic layer was concentrated in vacuo and the crude product was purified by chromatography on silica gel with  $\text{Et}_2\text{O}$ /Hexane 1:2 to yield 2.47 g (15 %) 15 of clean 4-(4-Bromo-butoxy)-piperidin-1-carboxylic acid tert-butyl ester, MS: 336 ( $\text{M}^+$ ).

**1.2b**

To an ice-cooled solution of 4.85 ml (55.73 mmol) 3-Bromo-1-propanol and 13.45 ml (59.9 mmol) of 2,6-Di-tert-butylpyridine in 45 ml of  $\text{CH}_2\text{Cl}_2$  was added at  $0^\circ\text{C}$  9.66 ml (58.5 mmol) of Trifluoromethanesulfonic anhydride. The reaction-mixture was stirred for 20 2.5h at  $0^\circ\text{C}$  and then concentrated under reduced pressure. The crude residue was dissolved in 30 ml of nitromethane. This solution was added dropwise within 10 min to a solution of 6 g (27.87 mmol) 4-Hydroxymethyl-piperidine-1-carboxylicacid tert-butylester and 12.56 ml (55.74 mmol) Di-tert-butylpyridine in 90ml of nitromethane. The mixture was stirred for 2h at  $60^\circ\text{C}$ , cooled to RT, diluted with EtOAc and washed with 1N HCl, 25  $\text{H}_2\text{O}$ , sat.  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$  again. The organic layer was concentrated in vacuo. The crude product was purified by chromatography on silica gel with  $\text{Et}_2\text{O}$ /hexane 1:2 yielding 6.27 g (33 %) of clean 4-(3-Bromo-propoxy methyl)-piperidin-1-carboxylic acid tert-butyl ester, MS: 336 ( $\text{M}^+$ ).

**1.3**

To a solution of 2.47 g (7.35 mmol) 4-(4-Bromo-butoxy)-piperidin-1-carboxylic acid tert-butyl ester in 10ml of  $\text{CH}_2\text{Cl}_2$  was added 20ml of 4N HCl in dioxane. The reaction-mixture was stirred for 2h at RT and then concentrated under reduced pressure. The crude residue was suspended several times with  $\text{Et}_2\text{O}$  and then dried in vacuo to yield 1.78 g (quantitative) of 4-(4-Brom-butoxy)-piperidine hydrogen chloride, MS: 236 ( $\text{M}^+$ ).

- 28 -

## 1.4

To a solution of 0.4 g (1.47 mmol) 4-(4-Brom-butoxy)-piperidine hydrogen chloride and 0.198ml (1.54 mmol) 4-chloro-benzoylchloride in 5ml of  $\text{CH}_2\text{Cl}_2$  was added 1 ml (5.87 mmol) of N-ethyldiisopropylamine. The reaction-mixture was stirred for 1h at RT, diluted with  $\text{Et}_2\text{O}$  and then washed with 1N HCl and water. The crude product was purified by chromatography on silica gel with EtOAc/hexane 1:1, to yield 459 mg (84 %) of clean 4-(4-Bromo-butoxy)-piperidin-1-yl)-(4-chloro-phenyl)-methanone, MS: 374 ( $\text{M}^+$ ).

## 1.5

To a solution of 220 mg (0.59 mmol) 4-(4-Bromo-butoxy)-piperidin-1-yl)-(4-chloro-phenyl)-methanone and 0.225 ml (2.35 mmol) of N-methylallylamine in 4ml of acetone was added 325 mg (2.35 mmol) of  $\text{K}_2\text{CO}_3$ . The reaction-mixture was stirred for 20h at  $50^\circ\text{C}$ , cooled down, filtered, and after concentration under reduced pressure the crude product was purified by chromatography on silica gel with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/25\%$  aqueous  $\text{NH}_3$  95.5 : 4 : 0.5 yielding 159 mg (74 %) of clean {4-[4-(Allyl-methyl-amino)-butoxy]-piperidin-1-yl)-(4-chloro-phenyl)-methanone, MS: 365 ( $\text{MH}^+$ ).

## 1.6

In analogy to example 1.4 and 1.5, reaction of 4-(4-Brom-butoxy)-piperidine hydrogen chloride with (4-chloro-phenyl)-acetyl chloride and N-methylallylamine yielded 1-{4-[4-(Allyl-methyl-amino)-butoxy]-piperidin-1-yl}-2-(4-chloro-phenyl)-ethanone, MS: 379 ( $\text{MH}^+$ ).

## 1.7

In analogy to example 1.4 and 1.5, reaction of 4-(4-Brom-butoxy)-piperidine hydrogen chloride with (4-chloro-phenyl)-acetyl chloride and 2-ethylamino-ethanol yielded 2-(4-Chloro-phenyl)-1-(4-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-piperidin-1-yl)-ethanone, MS: 397 ( $\text{MH}^+$ ).

## 1.8

In analogy to example 1.5, reaction of 4-(4-Bromo-butoxy)-piperidin-1-yl)-(4-chloro-phenyl)-methanone with 2-ethylamino-ethanol yielded (4-Chloro-phenyl)-(4-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-piperidin-1-yl)-methanone, MS: 383 ( $\text{MH}^+$ ).

## 30 1.9

In analogy to example 1.4 and 1.5, reaction of 4-(4-Brom-butoxy)-piperidine hydrogen chloride with 4-bromo-benzoylchloride and N-methylallylamine yielded {4-[4-(Allyl-methyl-amino)-butoxy]-piperidin-1-yl)-(4-bromo-phenyl)-methanone, MS: 409 ( $\text{MH}^+$ , 1Br).

- 29 -

## 1.10

In analogy to example 1.3, 1.4 and 1.5, reaction of 4-(3-Bromo-propoxy methyl)-piperidin-1-carboxylic acid tert-butyl ester with 4-bromo-benzoylchloride and N-methylallylamine followed by treatment with fumaric acid yielded {4-[3-(Allyl-methyl-amino)-propoxy]-piperidin-1-yl}-(4-bromo-phenyl)-methanone fumarate, MS: 395 (MH<sup>+</sup>, 1Br).

## 1.11

In analogy to example 1.4 and 1.5, reaction of 4-(4-Brom-butoxy)-piperidine hydrogen chloride with 4-chlorophenyl chloroformate and N-methylallylamine yielded 4-[4-(Allyl-methyl-amino)-butoxy]-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 381 (MH<sup>+</sup>).

## 1.12

In analogy to example 1.4 and 1.5, reaction of 4-(4-Brom-butoxy)-piperidine hydrogen chloride with 4-chlorophenyl chloroformate and 2-ethylamino-ethanol yielded 4-[4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy]-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 399 (MH<sup>+</sup>).

## 1.13

In analogy to example 1.4 and 1.5, reaction of 4-(4-Brom-butoxy)-piperidine hydrogen chloride with isobutyl chloroformate and N-methylallylamine yielded 4-[4-(Allyl-methyl-amino)-butoxy]-piperidine-1-carboxylic acid isobutyl ester, MS: 327 (MH<sup>+</sup>).

## 1.14

In analogy to example 1.4 and 1.5, reaction of 4-(4-Brom-butoxy)-piperidine hydrogen chloride with isobutyl chloroformate and 2-ethylamino-ethanol yielded 4-[4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy]-piperidine-1-carboxylic acid isobutyl ester, MS: 345 (MH<sup>+</sup>).

## 1.15

In analogy to example 1.4 and 1.5, reaction of 4-(4-Brom-butoxy)-piperidine hydrogen chloride with 4-chlorophenylsulfonyl chloride and N-methylallylamine yielded Allyl-{4-[1-(4-chloro-benzenesulfonyl)-piperidin-4-yloxy]-butyl}-methyl-amine, MS: 401 (MH<sup>+</sup>, 1Cl).

## 1.16

In analogy to example 1.4 and 1.5, reaction of 4-(4-Brom-butoxy)-piperidine hydrogen chloride with 4-bromophenylsulfonyl chloride and N-methylallylamine yielded Allyl-{4-[1-(4-bromo-benzenesulfonyl)-piperidin-4-yloxy]-butyl}-methyl-amine, MS: 445 (MH<sup>+</sup>, 1Br).

- 30 -

## 1.17

In analogy to example 1.3, 1.4 and 1.5, reaction of 4-(3-Bromo-propoxy methyl)-piperidin-1-carboxylic acid tert-butyl ester with 4N HCl, 4-bromophenylsulfonyl chloride and N-methylallylamine followed by treatment with fumaric acid yielded Allyl-{3-[1-(4-bromo-benzenesulfonyl)-piperidin-4-yloxy]-propyl}-methyl-amine fumarate, MS: 431 (MH<sup>+</sup>, 1Br).

## 1.18

In analogy to example 1.2a and 1.3, reaction of 4-Hydroxy-piperidine-1-carboxylic-acid tert-butyl ester and 1,6-dibromohexane followed by treatment with 4N HCl yielded 4-(6-Bromo-hexyloxy)-piperidine hydrochloride, MS: 264 (MH<sup>+</sup>, 1Br).

## 1.19

In analogy to example 1.2a, 1.5 and 1.3, reaction of 4-Hydroxy-piperidine-1-carboxylic-acid tert-butyl ester and 1,6-dibromohexane, N-methylallylamine followed by treatment with 4N HCl yielded Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine dihydrochloride, MS: 255 (MH<sup>+</sup>).

## 1.20

In analogy to example 1.2a, 1.5 and 1.3, reaction of 4-Hydroxy-piperidine-1-carboxylic-acid tert-butyl ester and 1,6-dibromohexane, N-methylcyclopropylamine followed by treatment with 4N HCl yielded Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine dihydrochloride, MS: 255 (MH<sup>+</sup>).

## Example 2

## 2.1

In analogy to example 1.2a, 1.3, 1.4 and 1.5, reaction of 4-Hydroxy-piperidine with 1,5-dibromopentane, (4-fluoro-phenyl)-acetyl chloride and N-methylallylamine yielded 1-{4-[5-(Allyl-methyl-amino)-pentyloxy]-piperidin-1-yl}-2-(4-fluoro-phenyl)-ethanone, MS: 377 (MH<sup>+</sup>).

## 2.2

In analogy to example 1.2a, 1.3, 1.4 and 1.5, reaction of 4-Hydroxy-piperidine with 1,5-dibromopentane, (4-fluoro-phenyl)-acetyl chloride and diethylamine yielded 1-[4-(5-Diethylamino-pentyloxy)-piperidin-1-yl]-2-(4-fluoro-phenyl)-ethanone, MS: 379 (MH<sup>+</sup>).

## 2.3

- 31 -

In analogy to example 1.2a, 1.3, 1.4 and 1.5, reaction of 4-Hydroxy-piperidine with 1,5-dibromopentane, (4-fluoro-phenyl)-acetyl chloride and N-(2-methoxyethyl)methylamine yielded 2-(4-Fluoro-phenyl)-1-(4-{5-[(2-methoxy-ethyl)-methyl-amino]-pentyloxy}-piperidin-1-yl)-ethanone, MS: 395 (MH<sup>+</sup>).

## 5    2.4

In analogy to example 1.2a, 1.3, 1.4 and 1.5, reaction of 4-Hydroxy-piperidine with 1,5-dibromopentane, (4-fluoro-phenyl)-acetyl chloride and N-methylcyclopropylamine yielded 1-{4-[5-(Cyclopropyl-methyl-amino)-pentyloxy]-piperidin-1-yl}-2-(4-fluoro-phenyl)-ethanone, MS: 377 (MH<sup>+</sup>).

10

**Example 3**

## 3.1

15    In analogy to example 1.7, 4-Hydroxymethyl-piperidine was converted to 2-(4-Chloro-phenyl)-1-(4-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxymethyl}-piperidin-1-yl)-ethanone, MS: 411 (MH<sup>+</sup>).

## 3.2

In analogy to example 1.6, 4-Hydroxymethyl-piperidine was converted to 1-{4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidin-1-yl}-2-(4-chloro-phenyl)-ethanone, MS: 393 (MH<sup>+</sup>).

## 20    3.3

In analogy to example 1.5, 4-Hydroxymethyl-piperidine was converted to {4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidin-1-yl}-(4-chloro-phenyl)-methanone, MS: 379 (MH<sup>+</sup>).

## 3.4

25    In analogy to example 1.8, 4-Hydroxymethyl-piperidine was converted to (4-Chloro-phenyl)-(4-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxymethyl}-piperidin-1-yl)-methanone, MS: 397 (MH<sup>+</sup>).

## 3.5

30    In analogy to example 1.11, 4-Hydroxymethyl-piperidine was converted to 4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 395 (MH<sup>+</sup>).

## 3.6

- 32 -

In analogy to example 1.12, 4-Hydroxymethyl-piperidine was converted to 4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxymethyl}-piperidine-1-carboxylic acid 4-chloro-phenyl ester. MS: 413.4 (M+H<sup>+</sup>)

## 3.7

- 5 In analogy to example 1.6 (following procedure 1.2b for the introduction of the bromopropoxy side chain with 3-bromo-1-propanol), 4-Hydroxymethyl-piperidine was converted to 1-{4-[3-(Allyl-methyl-amino)-propoxymethyl]-piperidin-1-yl}-2-(4-chlorophenyl)-ethanone, MS: 379 (MH<sup>+</sup>).

## 3.8

- 10 In analogy to example 1.7 (following procedure 1.2b for the introduction of the bromopropoxy side chain with 3-bromo-1-propanol), 4-Hydroxymethyl-piperidine was converted to 2-(4-Chloro-phenyl)-1-(4-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-piperidin-1-yl)-ethanone, MS: 397 (MH<sup>+</sup>).

## 3.9

- 15 In analogy to example 1.5 (following procedure 1.2b for the introduction of the bromopropoxy side chain with 3-bromo-1-propanol), 4-Hydroxymethyl-piperidine was converted to {4-[3-(Allyl-methyl-amino)-propoxymethyl]-piperidin-1-yl}-(4-chlorophenyl)-methanone, MS: 365 (MH<sup>+</sup>).

## 3.10

- 20 In analogy to example 1.8 (following procedure 1.2b for the introduction of the bromopropoxy side chain with 3-bromo-1-propanol), 4-Hydroxymethyl-piperidine was converted to (4-Chloro-phenyl)-(4-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-piperidin-1-yl)-methanone, MS: 383 (MH<sup>+</sup>).

## 3.11

- 25 In analogy to example 1.11 (following procedure 1.2b for the introduction of the bromopropoxy side chain with 3-bromo-1-propanol), 4-Hydroxymethyl-piperidine was converted to 4-[3-(Allyl-methyl-amino)-propoxymethyl]-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 381 (MH<sup>+</sup>).

## 3.12

- 30 In analogy to example 1.12 (following procedure 1.2b for the introduction of the bromopropoxy side chain with 3-bromo-1-propanol), 4-Hydroxymethyl-piperidine was converted to 4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 399 (MH<sup>+</sup>).



- 33 -

## Example 4

## 4.1

In analogy to example 1.6, 4-Piperidine-ethanol was converted to 1-(4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-ethanone, MS: 407 (MH<sup>+</sup>).

## 4.2

In analogy to example 1.7, 4-Piperidine-ethanol was converted to 2-(4-Chloro-phenyl)-1-[4-(2-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-ethyl)-piperidin-1-yl]-ethanone. MS: 425 (MH<sup>+</sup>).

## 10 4.3

In analogy to example 1.5, 4-Piperidine-ethanol was converted to (4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidin-1-yl)-(4-chloro-phenyl)-methanone, MS: 393 (MH<sup>+</sup>).

## 4.4

In analogy to example 1.8, 4-Piperidine-ethanol was converted to (4-Chloro-phenyl)-[4-(2-{4-[ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-ethyl)-piperidin-1-yl]-methanone, MS: 411 (MH<sup>+</sup>).

## 4.5

In analogy to example 1.11, 4-Piperidine-ethanol was converted to 4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 409 (MH<sup>+</sup>).

## 4.6

In analogy to example 1.12, 4-Piperidine-ethanol was converted to 4-(2-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-ethyl)-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 427 (MH<sup>+</sup>).

## 25 4.7

In analogy to example 1.13, 4-Piperidine-ethanol was converted to isobutyl-chloroformate to yield: 4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidine-1-carboxylic acid isobutyl ester, MS: 355 (MH<sup>+</sup>).

## 4.8

In analogy to example 1.14, 4-Piperidine-ethanol was converted to 4-(2-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-ethyl)-piperidine-1-carboxylic acid isobutyl ester, MS: 373 (MH<sup>+</sup>).

- 34 -

## 4.9

In analogy to example 1.6 (following procedure 1.2b for the introduction of the bromopropoxy side chain), 4-Piperidine-ethanol was converted to 1-(4-{2-[3-(Allyl-methyl-amino)-propoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-ethanone, MS: 393 (MH<sup>+</sup>).

## 5 4.10

In analogy to example 1.7 (following procedure 1.2b for the introduction of the bromopropoxy side chain), 4-Piperidine-ethanol was converted to 2-(4-Chloro-phenyl)-1-[4-(2-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-ethyl)-piperidin-1-yl]-ethanone, MS: 411 (MH<sup>+</sup>).

## 10 4.11

In analogy to example 1.5 (following procedure 1.2b for the introduction of the bromopropoxy side chain), 4-Piperidine-ethanol was converted to (4-{2-[3-(Allyl-methyl-amino)-propoxy]-ethyl}-piperidin-1-yl)-(4-chloro-phenyl)-methanone, MS: 379 (MH<sup>+</sup>).

## 4.12

15 In analogy to example 1.8 (following procedure 1.2b for the introduction of the bromopropoxy side chain), 4-Piperidine-ethanol was converted to (4-Chloro-phenyl)-[4-(2-{3-[ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-ethyl)-piperidin-1-yl]-methanone, MS: 397 (MH<sup>+</sup>).

## 4.13

20 In analogy to example 1.11 (following procedure 1.2b for the introduction of the bromopropoxy side chain), 4-Piperidine-ethanol was converted to 4-{2-[3-(Allyl-methyl-amino)-propoxy]-ethyl}-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 395 (MH<sup>+</sup>).

## 4.14

25 In analogy to example 1.12 (following procedure 1.2b for the introduction of the bromopropoxy side chain), 4-Piperidine-ethanol was converted to 4-(2-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-ethyl)-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 413 (MH<sup>+</sup>).

## 4.15

30 In analogy to example 1.6 (following procedure 1.2b for the introduction of the bromoethoxy side chain with 2-bromoethanol), 4-Piperidine-ethanol was converted to 1-(4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-ethanone, MS: 379 (MH<sup>+</sup>).

- 35 -

## 4.16

In analogy to example 1.7 (following procedure 1.2b for the introduction of the bromoethoxy side chain with 2-bromoethanol), 4-Piperidine-ethanol was converted to 1-(4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-ethanone,  
5 MS: 397 (MH<sup>+</sup>).

## 4.17

In analogy to example 1.5 (following procedure 1.2b for the introduction of the bromoethoxy side chain with 2-bromoethanol), 4-Piperidine-ethanol was converted to 1-(4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-ethanone,  
10 MS: 365 (MH<sup>+</sup>).

## 4.18

In analogy to example 1.8 (following procedure 1.2b for the introduction of the bromoethoxy side chain with 2-bromoethanol), 4-Piperidine-ethanol was converted to (4-Chloro-phenyl)-[4-(2-{2-[ethyl-(2-hydroxy-ethyl)-amino]-ethoxy}-ethyl)-piperidin-1-yl]-methanone, MS: 383 (MH<sup>+</sup>).  
15

## 4.19

In analogy to example 1.11 (following procedure 1.2b for the introduction of the bromoethoxy side chain with 2-bromoethanol), 4-Piperidine-ethanol was converted to 4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidine-1-carboxylic acid 4-chloro-phenyl ester,  
20 MS: 381 (MH<sup>+</sup>).

## 4.20

In analogy to example 1.12 (following procedure 1.2b for the introduction of the bromoethoxy side chain with 2-bromoethanol), 4-Piperidine-ethanol was converted to 4-(2-{2-[Ethyl-(2-hydroxy-ethyl)-amino]-ethoxy}-ethyl)-piperidine-1-carboxylic acid 4-chloro-phenyl ester, MS: 399 (MH<sup>+</sup>).  
25

## 4.21

In analogy to example 1.13 (following procedure 1.2b for the introduction of the bromoethoxy side chain with 2-bromoethanol), 4-Piperidine-ethanol was converted to 4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidine-1-carboxylic acid isobutyl ester, MS: 327  
30 (MH<sup>+</sup>).

## 4.22

In analogy to example 1.14 (following procedure 1.2b for the introduction of the bromoethoxy side chain with 2-bromoethanol), 4-Piperidine-ethanol was converted to 4-(2-{2-[Ethyl-(2-hydroxy-ethyl)-amino]-ethoxy}-ethyl)-piperidine-1-carboxylic acid isobutyl  
35 ester, MS: 345 (MH<sup>+</sup>).

- 36 -

## Example 5

- A solution of 0.153 mmol of amine dihydrochloride and 0.5 mmol triethylamine in 0.35 ml dry  $\text{CH}_2\text{Cl}_2$  was treated with 0.23 mmol isocyanate in 0.54 ml dry  $\text{CH}_2\text{Cl}_2$ . The solution was allowed to stand over night at room temperature. The resulting reaction mixture was evaporated and treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 %  $\text{HCOOH}$ )/water (0.1 %  $\text{HCOOH}$ ), 10 % to 95 % acetonitrile]. After evaporation the corresponding compound was obtained as a mixture of amino hydrochloride and formiate. The following compounds were obtained using the corresponding amines and isocyanates:

Example	Compound	MS $\text{MH}^+$	Amine	Isocyanate
5.1	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide	460	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Fluoro-3-trifluoromethylphenylisocyanate
5.2	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (2,4-difluoro-phenyl)-amide	410	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2,4-Difluorophenylisocyanate
5.3	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (2,4-dimethoxy-phenyl)-amide	434	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2,4 Dimethoxyphenylisocyanate
5.4	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-fluoro-phenyl)-amide	392	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Fluorophenylisocyanate
5.5	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-methoxy-phenyl)-amide	404	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Methoxyphenylisocyanate

- 37 -

5.6	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid p-tolylamide	388	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Methylphenyl-isocyanate
5.7	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-methoxy-2-methyl-phenyl)-amide	418	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Methoxy-2-Methylphenyl-isocyanate
5.8	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (2,4-dimethyl-phenyl)-amide	402	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2,4 Dimethyl-phenylisocyanate
5.9	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (3,4,5-trimethoxy-phenyl)-amide	464	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	3,4,5 Trimethoxy-phenylisocyanate
5.10	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (3,4-dimethyl-phenyl)-amide	402	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	3,4 Dimethyl-phenylisocyanate
5.11	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-acetyl-phenyl)-amide	416	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Acetylphenyl-isocyanate
5.12	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-butyl-phenyl)-amide	430	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Butylphenyl-isocyanate
5.13	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-methylsulfanyl-phenyl)-amide	420	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Methylmercapto-phenylisocyanate

- 38 -

5.14	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-isopropyl-phenyl)-amide	416	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Isopropylphenyl-isocyanate
5.15	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (3,4-dichloro-phenyl)-amide	442 (2 Cl)	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	3,4 Dichlorophenyl-isocyanate
5.16	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid (4-bromo-phenyl)-amide	452 (1 Br)	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Bromophenyl-isocyanate
5.17	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid naphthalen-2-ylamide	424	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2-Naphthyl-isocyanate
5.18	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid naphthalen-1-ylamide	424	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	1-Naphthyl-isocyanate
5.19	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid phenethyl-amide	402	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2-Phenylethyl-isocyanate

- 39 -

**Example 6**

A solution of 0.153 mmol of amine dihydrochloride in 0.35 ml dry dioxane was treated with 0.77 mmol (5 equivalents) Hünig's base and 0.2 mmol chloroformate in 0.54 ml dry dioxane. The solution was allowed to stand over night at room temperature and the resulting reaction mixture was treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation the corresponding compound was obtained as a mixture of amino hydrochloride and formiate. The following compounds were obtained using the corresponding amines and chloroformates:

Example	Compound	MS MH <sup>+</sup>	Amine	Chloroformate
6.1	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid ethyl ester	327	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Ethylchloroformate
6.2	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester	477	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	9-Fluorenylmethyl-chloroformate
6.3	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid methyl ester	313	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Methyl-chloroformate
6.4	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester	457 (3 Cl)	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2,2,2-Trichloro-1,1-Dimethylethyl-chloroformate
6.5	4-[6-(allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-nitro-phenyl ester	420	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Nitrophenyl-chloroformate

- 40 -

6.6	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid isobutyl ester	355	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Isobutyl-chloroformate
6.7	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid benzyl ester	389	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Benzyl-chloroformate
6.8	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid allyl ester	339	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Allylchloroformate
6.9	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid phenyl ester	375	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Phenyl-chloroformate
6.10	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid butyl ester	355	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Butylchloroformate
6.11	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-methoxycarbonyl-phenyl ester	433	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Methoxy-carbonylphenyl-chloroformate
6.12	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-fluorophenylester	393	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Fluorophenyl-chloroformate
6.13	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-bromophenyl ester	453 (1 Br)	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Bromophenyl-chloroformate



- 41 -

6.14	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-chlorophenyl ester	409 (1 Cl)	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Chlorophenyl-chloroformate
6.15	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid p-tolyl ester	389	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Tosyl-chloroformate

### Example 7

A solution of 1.5 mmol trichloromethyl-chloroformate (diphosgene) in 20 ml  $\text{CH}_2\text{Cl}_2$  was treated at 0 °C with 3 mmol 4-Trifluoromethyl-phenol and 3 mmol quinoline and then stirred for 3 h at room temperature. The reaction mixture was then cooled (0 °C) and a solution of 1 mmol Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine (the amine dihydrochloride was extracted with 1 N NaOH/  $\text{CH}_2\text{Cl}_2$ ) and 2.5 mmol pyridine in 3 ml  $\text{CH}_2\text{Cl}_2$  was added, followed by 1 mmol DMAP. The mixture was stirred over night at room temperature, evaporated and treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 %  $\text{HCOOH}$ )/water (0.1 %  $\text{HCOOH}$ ), 10 % to 95 % acetonitrile]. After evaporation 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid 4-trifluoromethyl-phenyl ester was obtained as a mixture of amino hydrochloride and formiate, MS: 443 ( $\text{MH}^+$ ).

**Example 8**

A solution of 0.135 mmol amine dihydrochloride in 0.75 ml dry  $\text{CH}_2\text{Cl}_2$  was treated with 4 equivalents of triethylamine followed by a solution of 0.175 mmol (1.3 equivalente) sulfamoylchloride in 0.25 ml dry  $\text{CH}_2\text{Cl}_2$ . The solution was allowed to stand over night at room temperature, was evaporated and then treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 %  $\text{HCOOH}$ )/water (0.1 %  $\text{HCOOH}$ ), 10 % to 95 % acetonitrile]. After evaporation of the corresponding fraction, the sulfamide was received as a mixture of amino hydrochloride and formiate. The following compounds were obtained using the corresponding amines and sulfamoylchlorides:

Example	Compound	MS $\text{MH}^+$	Amine	Sulfamoylchloride
8.1	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid benzylamide	424	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Benzyl-sulfamoylchloride
8.2	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid butylamide	390	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Butyl-sulfamoylchloride
8.3	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenethylamide	438	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Phenethyl-sulfamoylchloride
8.4	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (furan-2-ylmethyl)-amide	414	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Furan-2-ylmethyl-sulfamoylchloride
8.5	{4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonylamino}-acetic acid ethyl ester	420	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Chlorosulfonyl-amino-acetic acid ethyl ester

- 43 -

8.6	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid cyclohexylmethyl-amide	430	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Cyclohexylmethyl-sulfamoylchloride
8.7	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid cyclopropylamide	374	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Cyclopropyl-sulfamoylchloride
8.8	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,2,2-trifluoro-ethyl)-amide	416	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2,2,2-Trifluoroethyl-sulfamoylchloride
8.9	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (benzo[1,3]dioxol-5-ylmethyl)-amide	468	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Benzo[1,3]dioxol-5-ylmethyl-sulfamoylchloride
8.10	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid 4-fluoro-benzylamide	442	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Fluoro-benzyl-sulfamoylchloride
8.11	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-chloro-phenyl)-amide	444 (1 Cl)	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Chloro-phenyl-sulfamoyl chloride
8.12	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-chloro-phenyl)-amide	444 (1 Cl)	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Chloro-phenyl-sulfamoyl chloride
8.13	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-fluoro-phenyl)-amide	428	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Fluoro-phenyl-sulfamoyl chloride

- 44 -

8.14	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-fluoro-phenyl)-amide	428	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Fluoro-phenyl-sulfamoyl chloride
8.15	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-bromo-phenyl)-amide	488 (1 Br)	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Bromo-phenyl-sulfamoyl chloride
8.16	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-bromo-phenyl)-amide	488 (1 Br)	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Bromo-phenyl-sulfamoyl chloride
8.17	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (p-tolyl)-amide	424	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	p-tolyl-sulfamoylchloride
8.18	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (p-tolyl)-amide	424	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	p-tolyl-sulfamoylchloride
8.19	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3,4-difluoro-phenyl)-amide	446	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	3,4-Difluorophenyl-sulfamoyl chloride
8.20	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3,4-difluoro-phenyl)-amide	446	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	3,4-Difluorophenyl-sulfamoyl chloride
8.21	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-trifluoromethyl-phenyl)-amide	478	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Trifluoromethyl-phenyl-sulfamoylchloride

- 45 -

8.22	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-trifluoromethyl-phenyl)-amide	478	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Trifluoromethyl-phenyl-sulfamoylchloride
8.23	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3-fluoro-phenyl)-amide	428	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	3-Fluorophenyl-sulfamoylchloride
8.24	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3-fluoro-phenyl)-amide	428	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	3-Fluorophenyl-sulfamoylchloride
8.25	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-cyano-phenyl)-amide	435	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Cyanophenyl-sulfamoylchloride
8.26	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-cyano-phenyl)-amide	435	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Cyanophenyl-sulfamoylchloride
8.27	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,4-difluoro-phenyl)-amide	446	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2,4-Difluorophenyl-sulfamoylchloride
8.28	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,4-difluoro-phenyl)-amide	446	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2,4-Difluorophenyl-sulfamoylchloride
8.29	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-methoxy-phenyl)-amide	440	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Methoxyphenyl-sulfamoylchloride

- 46 -

8.30	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-methoxy-phenyl)-amide	440	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	4-Methoxyphenyl-sulfamoylchloride
8.31	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,5-difluoro-phenyl)-amide	446	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2,5-Difluorophenyl-sulfamoylchloride
8.32	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,5-difluoro-phenyl)-amide	446	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	2,5-Difluorophenyl-sulfamoylchloride
8.33	4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (phenyl)-amide	410	Cyclopropyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Phenyl-sulfamoylchloride
8.34	4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (phenyl)-amide	410	Allyl-methyl-[6-(piperidin-4-yloxy)-hexyl]-amine	Phenyl-sulfamoylchloride

- 47 -

**Example 9**

A solution of 3 g (10 mmol) 4-(6-Bromo-hexyloxy)-piperidine hydrochloride and 3.44 g (18 mmol) of Phenylsulfamoyl chloride in 100 ml dry  $\text{CH}_2\text{Cl}_2$  was treated with 6.95 ml (49.9 mmol) of triethylamine. The reaction was stirred for 4 h at RT, diluted with  $\text{CH}_2\text{Cl}_2$  and washed with water. The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated to yield 5.67 g (quantitative) of 4-(6-Bromo-hexyloxy)-piperidine-1-sulfonic acid phenylamide.

A solution of the amine (0.26 mmol; 1.5 equivalents) in 0.7 ml DMF was treated with 4-(6-Bromo-hexyloxy)-piperidine-1-sulfonic acid phenylamide (0.17 mmol; 1 equivalent) in 0.25 ml DMF, sodium iodide (1 equivalent; 0.17 mmol) and with Huenig's base (1 equivalent; 0.17 mmol). The reaction mixture was shaken over night at  $60^\circ\text{C}$ , then treated with 0.2 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 %  $\text{HCOOH}$ )/water (0.1 %  $\text{HCOOH}$ ), 10 % to 95 % acetonitrile]. After evaporation of the corresponding fraction, the compound was received as a mixture of amino hydrobromide and formiate. The following compounds were obtained using the corresponding amines:

Example	Compound	MS $\text{MH}^+$	Amine
9.1	4-(6-Azepan-1-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide	438	Azepane
9.2	4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-piperidine-1-sulfonic acid phenylamide	428	(2-Methoxy-ethyl)-methyl-amine
9.3	4-[6-(Ethyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	398	Ethyl-methyl-amine
9.4	4-[6-(2-Methyl-piperidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	438	2-Methyl-piperidine
9.5	4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-piperidine-1-sulfonic acid phenylamide	414	(2-Hydroxy-ethyl)-methyl-amine
9.6	{Methyl-[6-(1-phenylsulfamoyl-piperidin-4-yloxy)-hexyl]-amino}-acetic acid ethyl ester	456	Amino-acetic acid ethyl ester

- 48 -

9.7	4-[6-(Butyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	426	Butyl-methyl-amine
9.8	4-(6-Diallylamino-hexyloxy)-piperidine-1-sulfonic acid phenylamide	436	Diallylamine
9.9	4-(6-Pyrrolidin-1-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide	410	Pyrrolidine
9.10	4-[6-(Methyl-prop-2-ynyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	408	Methyl-prop-2-ynyl-amine
9.11	4-(6-Piperidin-1-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide	424	Piperidine
9.12	4-[6-(Ethyl-isopropyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	426	Ethyl-isopropyl-amine
9.13	4-(6-Morpholin-4-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide	426	Morpholine
9.14	4-[6-(Isopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	412	Isopropyl-methyl-amine
9.15	4-[6-(3,6-Dihydro-2H-pyridin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	422	3,6-Dihydro-2H-pyridine
9.16	4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-piperidine-1-sulfonic acid phenylamide	428	Ethyl-(2-hydroxy-ethyl)-amine
9.17	4-(6-Dimethylamino-hexyloxy)-piperidine-1-sulfonic acid phenylamide	384	Dimethylamine
9.18	4-[6-(Methyl-propyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	412	Methyl-propyl-amine
9.19	4-(6-Diethylamino-hexyloxy)-piperidine-1-sulfonic acid phenylamide	412	Diethylamine



- 49 -

9.20	4-(6-Thiomorpholin-4-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide	442	Thiomorpholine
9.21	4-[6-(Butyl-ethyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	440	Butyl-ethyl-amine
9.22	4-(6-Thiazolidin-3-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide	428	Thiazolidine
9.23	4-[6-(4-Hydroxy-piperidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	440	4-Hydroxy-piperidine
9.24	4-[6-(4-Methyl-piperazin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	439	4-Methyl-piperazine
9.25	4-[6-(4-Hydroxymethyl-piperidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	454	4-Hydroxymethyl-piperidine
9.26	4-[6-(Cyclopropylmethyl-propyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	452	Cyclopropylmethyl-propyl-amine
9.27	4-[6-(3-Hydroxy-piperidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	440	3-Hydroxy-piperidine
9.28	4-[6-(Cyclohexyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	452	Cyclohexyl-methyl-amine
9.29	4-[6-(3-Dimethylamino-pyrrolidin-1-yl)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	453	3-Dimethylamine-pyrrolidine
9.30	4-(6-Azetidin-1-yl-hexyloxy)-piperidine-1-sulfonic acid phenylamide	396	Azetidine
9.31	4-[6-(Cyclopropylmethyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid phenylamide	424	Cyclopropylmethyl-methyl-amine

- 50 -

## Example 10

Sulfamoyl chlorides were prepared according to the following procedure. 3 equivalents of the corresponding amine were dissolved in  $\text{CH}_2\text{Cl}_2$  (1 ml/mmol) and placed in an ice bath. A solution of chlorosulfonic acid (1 eq.) in  $\text{CH}_2\text{Cl}_2$  (0.5 ml / mmol) was added slowly (30 min). The reaction mixture was stirred at  $0^\circ\text{C}$  for a further 30 min. Afterwards, the ice bath was removed and the stirring was continued for 1 h at room temperature. The precipitate was collected by filtration and dried under high vacuum. This salt was suspended in toluene (1 ml / mmol amine) and  $\text{PCl}_5$  (1 eq) was added. The mixture was stirred at  $75^\circ\text{C}$  for 2 h, cooled to room temperature and filtered. The solid residue was washed with toluene. The filtrate was evaporated and dried under high vacuum. The crude sulfamoyl chloride was used in the next step without further purification. The following sulfamoyl chlorides were prepared from the corresponding amine:

Sulfamoylchloride	Amine
Benzylsulfamoyl chloride	Benzylamine
Phenylsulfamoyl chloride	Aniline
2,4-Difluoro-phenylsulfamoyl chloride	2,4-Difluoroaniline
2,5-Difluoro-phenylsulfamoyl chloride	2,5-Difluoroaniline
3,4-Difluoro-phenylsulfamoyl chloride	3,4-Difluoroaniline
3-Fluoro phenyl-sulfamoyl chloride	3-Fluoroaniline
4-Fluoro-phenylsulfamoyl chloride	4-Fluoroaniline
4-Chloro-phenylsulfamoyl chloride	3-Chloroaniline
4-Bromo-phenylsulfamoyl chloride	3-Bromoaniline
4-Methyl-phenylsulfamoyl chloride	4-Methylaniline
4-trifluoromethyl-phenylsulfamoyl chloride	4-Trifluoromethylaniline
4-Cyano-phenylsulfamoyl chloride	4-Cyanoaniline
4-Methoxy-phenylsulfamoyl chloride	4-Methoxyaniline
Butylsulfamoyl chloride	Butylamine

- 51 -

Phenethylsulfamoyl chloride	Phenethylamine
Cyclohexylmethylsulfamoyl chloride	Aminomethylcyclohexane
Cyclopropylsulfamoyl chloride	Cyclopropylamine
2,2,2-Trifluoroethylsulfamoyl chloride	2,2,2-Trifluoroethylamine
4-Fluoro-benzylsulfamoyl chloride	4-Fluorobenzylamine
Furan-2-ylmethylsulfamoyl chloride	Furan-2-ylmethylamine
Benzo[1,3]dioxol-5-ylmethylsulfamoyl chloride	Benzo[1,3]dioxol-5-ylmethylamine

**Example 11**

Glycine ethyl ester hydrochloride (1 eq.) was dissolved in  $\text{CH}_3\text{CN}$  and placed in an ice bath. Sulfuryl chloride (3 eq.) was added slowly (20 min). The reaction mixture was stirred at room temperature for 15 min and at 65 °C for 20 h. The solvent was evaporated and the residue was dried under high vacuum to yield Chlorosulfonylamino-propionic acid ethyl ester. The crude sulfamoyl chloride was used in the next step without further purification.

- 52 -

Example A

Tablets containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per tablet</u>
Compound of formula I	10.0 - 100.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

5

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per capsule</u>
Compound of formula I	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

Example C

10 Injection solutions can have the following composition:

Compound of formula I	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Water for injection solutions	ad 1.0 ml

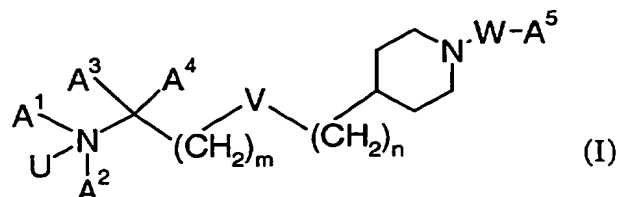
EPO - Munich  
22

08. Sep. 2000

- 53 -

Claims

## 1. Compounds of formula (I)



wherein

5 U is O or a lone pair,

V is O, -CH<sub>2</sub>-, -CH=CH-, or -C≡C-,

m and n independently from each other are 0 to 7 and m+n is 0 to 7,

W is CO, COO, CONR<sup>1</sup>, CSO, CSNR<sup>1</sup>, SO<sub>2</sub>, or SO<sub>2</sub>NR<sup>1</sup>, with the proviso that:

- 10 a) V is not -CH<sub>2</sub>- if W is CO,  
 b) m+n is 1 to 2 if V is -CH<sub>2</sub>- and W is SO<sub>2</sub>,  
 c) m=n=0 if V is -CH=CH- and W is CO or SO<sub>2</sub>,  
 d) m is 1 to 7 if V is O,  
 e) n is 1 to 6 or m+n is 1 to 3 if V is O and W is CO or SO<sub>2</sub>,

A<sup>1</sup> is H, lower-alkyl or lower-alkenyl,15 A<sup>2</sup> is cycloalkyl, cycloalkyl-lower-alkyl, lower-alkenyl, lower alkynyl, or lower-alkyl optionally substituted with hydroxy, lower-alkoxy or lower-alkoxy-carbonyl,A<sup>3</sup> and A<sup>4</sup> are hydrogen or lower-alkyl, or

A<sup>1</sup> and A<sup>2</sup> or A<sup>1</sup> and A<sup>3</sup> are bonded to each other to form a ring  
 and -A<sup>1</sup>-A<sup>2</sup>- or -A<sup>1</sup>-A<sup>3</sup>- are lower-alkylene or lower-alkenylene, optionally  
 20 substituted by R<sup>2</sup>, in which one -CH<sub>2</sub>- group of -A<sup>1</sup>-A<sup>2</sup>- or -A<sup>1</sup>-A<sup>3</sup>- can  
 optionally be replaced by NR<sup>3</sup>, S, or O,

A<sup>5</sup> is lower-alkyl optionally substituted with halogen, lower-alkenyl, lower-  
 alkoxy-carbonyl-lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl, aryl-  
 lower-alkyl, heteroaryl, or heteroaryl-lower-alkyl,

25 R<sup>2</sup> is lower-alkyl, hydroxy, hydroxy-lower-alkyl, or N(R<sup>4</sup>,R<sup>5</sup>),

- 54 -

$R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  independently from each other are hydrogen or lower-alkyl, and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

2. Compounds according to claim 1, wherein U is a lone pair.
3. Compounds according to any of claims 1 to 2, wherein V is O.
- 5 4. Compounds according to any of claims 1 to 3, wherein W is CO, COO, CONR<sup>1</sup>, SO<sub>2</sub>, or SO<sub>2</sub>NR<sup>1</sup> and R<sup>1</sup> is hydrogen.
5. Compounds according to any of claims 1 to 4, wherein W is CO, COO, or SO<sub>2</sub>NR<sup>1</sup> and R<sup>1</sup> is hydrogen.
6. Compounds according to any of claims 1 to 5, wherein n is 0 to 2.
- 10 7. Compounds according to any of claims 1 to 6, wherein m is 1 to 5.
8. Compounds according to any of claims 1 to 7, wherein A<sup>1</sup> is methyl, ethyl or 2-propenyl.
9. Compounds according to any of claims 1 to 8, wherein A<sup>2</sup> is methyl, n-propyl, i-propyl, n-butyl, 2-propenyl, 2-propinyl, cyclopropyl, cyclohexyl, cyclopropyl-methylene, 15 or ethyl optionally substituted with hydroxy, methoxy, or ethoxycarbonyl.
10. Compounds according to any of claims 1 to 9, wherein A<sup>2</sup> is 2-hydroxy-ethyl, 2-propenyl, or cyclopropyl.
11. Compounds according to any of claims 1 to 7, wherein A<sup>1</sup> and A<sup>2</sup> are bonded to each other to form a ring and -A<sup>1</sup>-A<sup>2</sup>- is lower-alkylene or lower-alkenylene, optionally 20 substituted by R<sup>2</sup>, in which one -CH<sub>2</sub>- group of -A<sup>1</sup>-A<sup>2</sup>- can optionally be replaced by NR<sup>3</sup>, S, or O, wherein R<sup>2</sup> is lower-alkyl, hydroxy, hydroxy-lower-alkyl, or N(lower-alkyl)<sub>2</sub>, and R<sup>3</sup> is lower alkyl.
12. Compounds according to claim 11, wherein R<sup>2</sup> is methyl, hydroxy, 2-hydroxy-ethyl, or N(CH<sub>3</sub>)<sub>2</sub>, and R<sup>3</sup> is methyl.
- 25 13. Compounds according to any of claims 1 to 12, wherein A<sup>3</sup> is hydrogen.
14. Compounds according to any of claims 1 to 12, wherein A<sup>4</sup> is hydrogen.

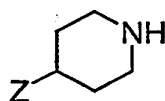
- 55 -

15. Compounds according to any of claims 1 to 14, wherein A<sup>5</sup> is lower-alkyl optionally substituted by one or more substituents selected from the group consisting of fluorine and chlorine, lower-alkenyl, cycloalkyl, cycloalkyl-lower-alkyl, lower-alkoxy-carbonyl-lower-alkyl, naphthyl, furyl-methylene, or phenyl, benzyl or phenyl-ethylene, optionally substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, CN, CF<sub>3</sub>, NO<sub>2</sub>, lower-alkyl, lower-alkoxy, thio-lower-alkoxy, lower-alkyl-carbonyl, lower-alkoxy-carbonyl, and dioxo-lower-alkylene.
16. Compounds according to any of claims 1 to 15, wherein A<sup>5</sup> is lower-alkyl, cycloalkyl-lower-alkyl, or phenyl or benzyl optionally substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, and CF<sub>3</sub>.
17. Compounds according to any of claims 1 to 16, wherein A<sup>5</sup> is n-butyl, i-butyl, cyclohexyl-methylene, phenyl, 4-chloro-phenyl, 4-bromo-phenyl, 2,5-difluoro-phenyl, 3,4-difluoro-phenyl, 4-trifluoromethyl-phenyl, or 4-chloro-benzyl.
18. A compounds according to any of claims 1 to 17, selected from the group consisting of
- Allyl-{4-[1-(4-chloro-benzenesulfonyl)-piperidin-4-yloxy]-butyl}-methyl-amine,  
Allyl-{3-[1-(4-bromo-benzenesulfonyl)-piperidin-4-yloxy]-propyl}-methyl-amine,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-carboxylic acid isobutyl ester,  
{4-[4-(Allyl-methyl-amino)-butoxy]-piperidin-1-yl}-(4-chloro-phenyl)-methanone,  
1-(4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidin-1-yl)-2-(4-chloro-phenyl)-ethanone,  
(4-{2-[4-(Allyl-methyl-amino)-butoxy]-ethyl}-piperidin-1-yl)-(4-chloro-phenyl)-methanone,  
(4-{2-[2-(Allyl-methyl-amino)-ethoxy]-ethyl}-piperidin-1-yl)-(4-chloro-phenyl)-methanone,  
{4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidin-1-yl}-(4-chloro-phenyl)-methanone,  
{4-[3-(Allyl-methyl-amino)-propoxymethyl]-piperidin-1-yl}-(4-chloro-phenyl)-methanone,  
4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-piperidine-1-carboxylic acid 4-chloro-phenyl ester,  
4-[4-(Allyl-methyl-amino)-butoxymethyl]-piperidine-1-carboxylic acid 4-chloro-phenyl ester,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid butylamide,  
4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid cyclohexylmethyl-amide,

- 56 -

- 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-chloro-phenyl)-amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-bromo-phenyl)-amide,  
 5 4-[6-(Cyclopropyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (3,4-difluoro-phenyl)-amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (4-trifluoromethyl-phenyl)-amide,  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (2,5-difluoro-phenyl)-  
 10 amide, and  
 4-[6-(Allyl-methyl-amino)-hexyloxy]-piperidine-1-sulfonic acid (phenyl)-amide,  
 and pharmaceutically acceptable salts thereof.

19. A process for the manufacture of compounds according to any of claims 1 to 18, which process comprises reacting a compound of formula (II)



15

wherein Z is  $(A^1, A^2)N-C(A^3, A^4)-(CH_2)_m-V-(CH_2)_n-$ ,  $X-CH_2-(CH_2)_m-V-(CH_2)_n-$ ,  $HO(CH_2)_n-$ , or  $HOOC(CH_2)_n-$ , wherein X is chlorine, bromine, iodine, methanesulfonyl, or toluenesulfonyl, and  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ , V, m and n are as defined in claim 1,

with  $ClSO_2-A^5$ ,  $ClCOO-A^5$ ,  $ClCSO-A^5$ ,  $OCN-A^5$ ,  $SCN-A^5$ ,  $HOOC-A^5$ , or  $ClSO_2NR^1-A^5$ ,  
 20 wherein  $A^5$  is as defined in claim 1.

20. Compounds according to any of claims 1 to 18 when manufactured by a process according to claim 19.

21. Pharmaceutical compositions comprising a compound according to any of claims 1 to 18 and a pharmaceutically acceptable carrier and/or adjuvant.

25 22. Compounds according to any of claims 1 to 18 for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gall stones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose  
 30 tolerance and diabetes.



- 57 -

23. A method for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, which method  
5 comprises administering a compound according to any of claims 1 to 18 to a human being or animal.

24. The use of compounds according to any of claims 1 to 18 for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones,  
10 tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance, and diabetes.

25. The use of compounds according to any of claims 1 to 18 for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases,  
15 mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes.

26. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.

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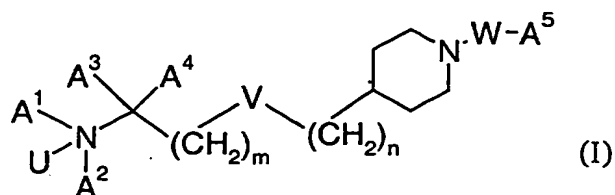
- 58 -

EPO - Munich  
22

08. Sep. 2000

Abstract

The present invention relates to compounds of formula (I)



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wherein U, V, W, A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup>, A<sup>4</sup>, A<sup>5</sup>, m and n are as defined in the description and claims and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

The compounds are useful for the treatment and/or prophylaxis of diseases which are associated with 2,3-oxidosqualene-lanosterol cyclase such as hypercholesterolemia,

10 hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and treatment and/or prophylaxis of impaired glucose tolerance and diabetes.

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